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Health outcomes of asymptomatic HIV-infected pregnant women initiating antiretroviral therapy at different baseline CD4 counts in Ethiopia

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A B S T R A C T

Objective: To compare health outcomes following initiation of antiretroviral therapy (ART) for asymptomatic HIV-infected pregnant women at different CD4 levels.
Methods: We analyzed data from 706 asymptomatic HIV-infected Ethiopian women initiating ART during pregnancy between February 2012 and October 2016. The outcomes evaluated were CD4 gain, CD4 normalization (CD4 count $\geq$750 cells/mm^3) and occurrence of HIV-related clinical events after twelve months of treatment.
Result: On average, CD4 count (cells/mm^3) increased from 391 (95% CI: 372–409) at baseline to 523 (95% CI: 495–551) after twelve months of treatment. Rate of CD4 gain was higher among women with baseline CD4 between 350 and 499 compared to CD4 $\geq$500 (207 versus 6, p < 0.001). But women with baseline CD4 between 350 and 499 could not catch up with women with CD4 $\geq$500. Women with baseline CD4 $\geq$500 had significantly higher likelihood of achieving CD4 normalization as compared to those with CD4 between 350 and 499 (AOR = 0.32, 95% CI: 0.13–0.76). No strong evidence of differential risk in the occurrence of HIV-related clinical events.
Conclusion: Starting ART for asymptomatic HIV-infected women with CD4 count $\geq$500 cells/mm^3 was beneficial to preserve or recover immunity after 12 months of treatment in a resource limited setting.
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Introduction

Antiretroviral therapy (ART) is effective in reducing mortality (Detels et al., 1998), and preventing mother-to-child transmission (MTCT) (CDC, 1994; Connor et al., 1994) and sexual transmission of HIV (Cohen et al., 2011). However, the optimal time to start treatment has been a topic of debate (WHO, 2016), as a result, HIV treatment guidelines have been regularly revised to balance risks and benefits of treatment. Initiation of ART immediately after diagnosis is currently recommended (WHO, 2016; Günthard et al., 2016; Ryom et al., 2016) following reports of clinical trials demonstrating the benefit of starting ART as early as possible

(Kitahata et al., 2009; Group TAS, 2015; Group ISS, 2015; O'Connor et al., 2016).

The effectiveness of ART in actual clinical settings might be inferior to what is reported by clinical trials, because clinical trial participants are more likely to be adherent to treatment than those treated in actual program settings. The benefit of early ART might even be very minimal among young asymptomatic adults with high level of CD4 count, as they have poor treatment adherence and retention (Nachega et al., 2014; Grimsrud et al., 2015; Hu et al., 2017), which could increase drug resistance (Meresse et al., 2014), and impact the potential benefit of early ART (Hu et al., 2017). In fact, a sub-group analysis of a clinical trial among adults aged below 30 years with CD4 count above 500 cells/mm^3 showed that those initiated treatment and those deferred treatment have similar rate of disease progression in the first 18 months (Schechter, 2018). This finding demonstrates that the benefit of

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early ART is not uniform across different patient groups. Therefore, observational studies are essential to clarify concerns of early initiation of ART. There are also reports indicating a greater risk of adverse outcomes (Nansseu and Bigna, 2017; Jose et al., 2014) associated with early ART initiation. Although newest antiretroviral drugs are more tolerable and have fewer side effects, they are not commonly used in low income settings.

The burden of HIV/AIDS in Ethiopia is substantial. It is estimated that 665,116 (1.1%) adults were living with the virus in 2016 and the majority (61.5%) were women (UNAIDS, 2016). At the time of the study, indication to start ART for adults in Ethiopia was based on CD4 count or disease progression. However, pregnant women were started on ART up on diagnosis to prevent mother-to-child transmission (Federal HIV Prevention and Control Office of Ethiopia, 2014). The CD4 count threshold for initiating treatment for asymptomatic adults was 350 cells/mm^3, but was subsequently increased to 500 cells/mm^3 in 2013, and ART was recommended for all HIV infected adults in 2017 (Federal Minstry of Health Ethiopia, 2017). The recommended type of ART has also been regularly revised; at the time of the study, a combination of tenofovir, lamivudine and efavirenz (TDF-3TC-EFV) was the preferred first line ART. Prophylaxes including co-trimoxazole and isoniazid preventive therapy have been routinely provided to prevent opportunistic infections. Treatment response was monitored by CD4 count measured every six months (Federal Ministry of Health Ethiopia, 2017). Evaluating the health benefits of ART for HIV-infected but asymptomatic Ethiopian women with high level of CD4 counts is important. To our knowledge, there are no previous Ethiopian studies addressing these questions. Therefore, the main objective of our study was to evaluate the clinical and immunological outcomes of asymptomatic HIV-infected pregnant women who initiated ART at different CD4 levels in Ethiopia.

Materials and methods

Study population

The study was conducted in three hospitals and six health centers in Addis Ababa, Ethiopia. Information was obtained from clinical charts and ART databases of HIV-infected pregnant women attending prenatal care follow-up between February 2012 and October 2016. The clinical charts of 926 HIV-infected women who initiated ART during pregnancy were reviewed. We excluded HIV-infected pregnant women who had missing information about the type or timing of ART initiation, baseline CD4 count and WHO stage at the time of ART initiation. Women with HIV related clinical symptoms at the time of ART initiation, and those who did not return after HIV diagnoses were also excluded from the analysis. This left 706 HIV-infected asymptomatic pregnant women eligible for analysis of prospective HIV-related clinical events. Follow-up CD4 measurement was available for 668 women after six months and 297 women after twelve months of ART initiation (Figure 1). This historical chart review was regarded as clinical practice and outcome assessment and therefore did not require written consent. The study was approved by the Norway Regional Committees of Medical and Health Research Ethics of South/East Norway, Jimma University Ethical Review Board, and Addis Ababa City Administration Health Bureau.

Exposure variables

The main exposure variable was baseline CD4 count, which was measured at the time of ART initiation. Baseline CD4 count was categorized as less than 350 cells/mm^3, between 350 and 499 cell/mm^3 and 500 cells/mm^3 or more. We also evaluated the role of the type of ART regimen. According to the Ethiopian treatment guideline, the first drug of choice was a combination of tenofovir,
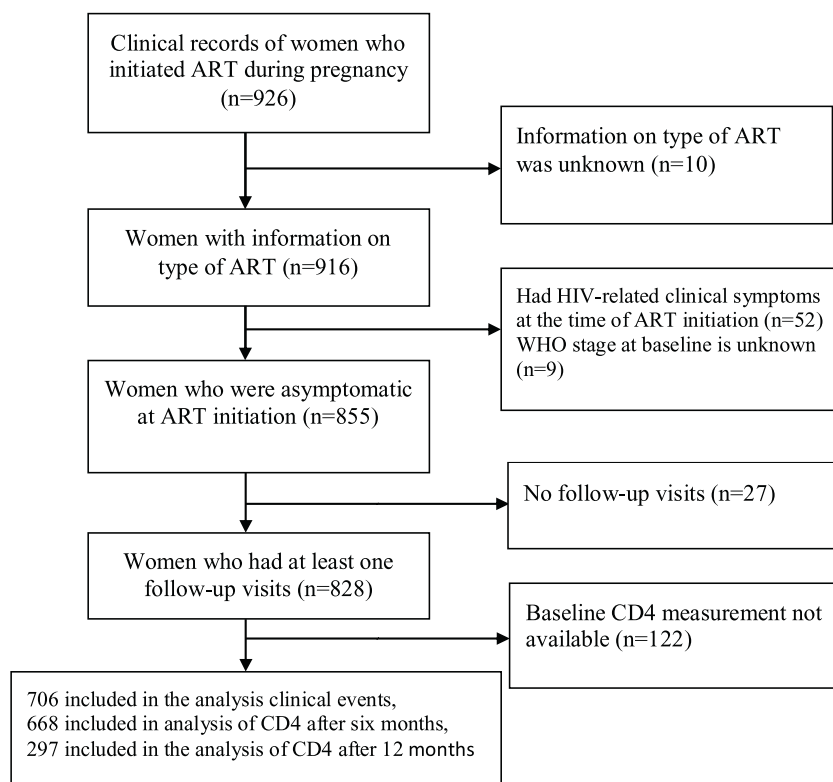
Figure 1. Flow diagram showing study inclusion and exclusions.
Legend: ART: antiretroviral therapy, WHO: World Health Organization.

lamivudine and efavirenz (TDF-3TC-EFV). Alternatives include a combination of tenofovir, lamivudine and nevirapine (TDF-3TC-NVP), zidovudine, lamivudine and nevirapine (ZDV-3TC-NVP) and zidovudine, lamivudine and efavirenz (ZDV-3TC-EFV). We categorized the type of ART as TDF-3TC-EFV compared to all other ART types (TDF-3TC-NVP, ZDV-3TC-NVP and ZDV-3TC-EFV).

Outcomes

The outcomes evaluated were average CD4 gain, CD4 normalization and incidence of HIV-related clinical events after twelve months of treatment. To define CD4 normalization, different studies used different cutoff points, ranging from 500 to 900 cells/mm³ (Gras et al., 2007; Le et al., 2013; García et al., 2004). Two Ethiopian studies reported 723 and 775 cells/mm³ as median CD4 counts of HIV-free healthy Ethiopian adults (Tsegaye et al., 1999; Abuye et al., 2005). We therefore defined CD4 normalization as achieving CD4 counts of at least 750 cells/mm³. The WHO clinical staging categorizes HIV infection into four stages (stage I–IV), stage one indicates that the patient has no HIV-related clinical symptoms or mild symptoms, and stage four indicates severe form of HIV-related illnesses including malignancies (WHO, 2013). Long-term outcomes, such as AIDS-defining illnesses and death were rare, in part due to the short follow-up period. As a result, occurrences of any WHO stage II–IV clinical events during our follow-up period were combined for the analysis.

Covariates

Additional information was gathered on maternal background characteristics likely to be associated with maternal immunologic and clinical outcomes. These included age, gestational week, level of education (no education, primary, secondary and tertiary), marital status (married and other), and weight in kilograms at the time of treatment initiation. We also gathered information on hemoglobin level (mg/dl) at the time of treatment initiation and self-reported adherence to treatment (missing less than 5% of the prescribed pills, categorized as "good", missing between 5 to 20% "fair" and missing more than 20% "poor").

Statistical analysis

We compared background characteristics of women by baseline CD4 category using chi-square for categorical covariates or Kruskal-Wallis test for continuous covariates. We used linear regression to examine the associations of baseline CD4 level and types of ART initiated with change in CD4 count at six and twelve months, reporting mean difference and 95% confidence intervals (CIs). We ran logistic regression to evaluate associations of baseline CD4 count and type of ART regimen with the probability of CD4 normalization, reporting odds ratio (OR) and 95% CIs. Cox-proportional hazard regression model was used to evaluate associations of baseline CD4 level and type of ART regimen with incident HIV-related clinical events, reporting hazard ratios (HRs) and 95% CIs. We censored follow-up time for each woman at the first registration of a WHO stage II to stage IV HIV-related clinical event, at the last visit, treatment interruption for more than 3 months, or after twelve months (end of follow-up). The multivariable analyses were adjusted for known covariates including age, gestational age, weight, marital status, education, hemoglobin level and adherence to treatment. In addition, baseline CD4 count and type of ART were adjusted for each other. Covariates

Table 1
Characteristics of 706 HIV infected asymptomatic pregnant Ethiopian women by baseline CD4 count category.

Characteristics	Total	Baseline CD4 category			
	(n = 706)	<350 cells/mm³ (n = 373)	350–499 cells/mm³ (n = 145)	>500 cells/mm³ (n = 188)	P-value[a]
Age in years (median + IQR)	28 (25–30)	28 (25–30)	28 (25–30)	27 (24–30)	0.02[b]
Gestational age in weeks at ART initiation (median + IQR)	20 (15–27)	21 (16–28)	20 (15–26)	19 (13–26)	0.04[b]
Marital status					
Married	659 (93)	340 (91.2)	137 (94.5)	182 (96.8)	0.04
Others	44 (6)	31 (8.3)	7 (4.8)	6 (3.2)	
Unknown	3 (0.4)	2 (0.5)	1 (0.7)	0 (0)	
Educational status					
No education	60 (9)	26 (7.0)	15 (10.3)	19 (10.1)	0.54
Primary	188 (27)	96 (25.7)	40 (27.6)	52 (27.7)	
Secondary	188 (27)	103 (27.6)	35 (24.1)	50 (26.6)	
Higher	51 (7)	32 (8.6)	7 (4.8)	12 (6.4)	
Unknown	219 (31)	116 (8.6)	48 (33.1)	55 (29.3)	
Baseline weight in kg (median ± IQR)	56 (50–64)	56 (50–62.5)	56 (51–62)	56 (50–65)	0.87b
Hemoglobin in mg/dl (median ± IQR)	12 (11–13)	12 (11–13)	12 (11–13)	12 (12–13)	0.001[b]
Adherence to treatment					
Good	612 (87)	318 (85.3)	130 (89.7)	164 (87.2)	0.47
Fair	38 (5)	21 (5.6)	7 (4.8)	10 (5.3)	
Poor	42 (6)	28 (7.5)	6 (4.1)	8 (4.3)	
Unknown	14 (2)	6 (1.6)	2 (1.4)	6 (3.2)	
Types of ART initiated					
TDF-3TC-EFV	569 (81)	258 (69.2)	137 (94.5)	174 (92.6)	<0.001
Other ART types[c]	137 (19)	115 (29.8)	8 (5.5)	14 (7.4)	

Data are n (%) or median (IQR). ZDV: zidovudine, 3TC: lamivudine, NVP: nevirapine, EFV: efavirenz, TDF: tenofovir, ART: antiretroviral therapy, IQR: interquartile range.
[a] Statistical tests did not consider missing values.
[b] Kruskal-Wallis tests, the rest are chi-square test results.
[c] Other type of ARTs which include: TDF–3TC-NVP, ZDV-3TC-NVP or ZDV-3TC-EFV.
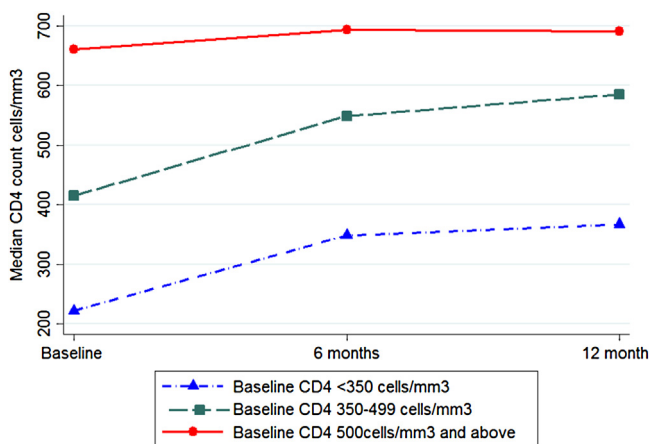
were categorized as indicated in Table 1 and entered using dummy variables. Most of the covariates had some missing values (ranging from 31% for level of education to 2% adherence to treatment). We therefore imputed missing values of covariates using chained equations, imputing a total of 20 datasets. The imputation model included all exposures, covariates, and outcome variables. We observed similar results in the multiple imputation and complete-case analyses. We report the results based on the imputed data as main results, while the findings from the complete-case analysis are presented in the supplement. The analyses were conducted using STATA version 13 (Stata Corp., College Station, TX).

Result

A total of 706 HIV-infected asymptomatic (WHO Stage I) women initiating ART during pregnancy were included in the analysis of occurrence of HIV-related clinical events. Background characteristics of women included (n = 706) and excluded (n = 220) from the analysis were largely similar, except that excluded women were younger and less compliant to treatment (Supplemental Table 1). Median age at ART initiation was 28 years (IQR: 25–30) and median gestational week at initiation was 20 weeks (IQR: 15–27). The majority of women (80.5%) initiated TDF-3TC-EFV. Women with baseline CD4 count $\geq$500 cells/mm^3 were younger and had higher hemoglobin level than women with CD4 below 500 cells/mm^3. The distributions of other background characteristics were largely similar across baseline CD4 levels (Table 1). The distribution of background characteristics of the subsample of women included in the evaluation of CD4 recovery at 6 months (n = 668) and 12 months (n = 297) after treatment initiation is presented in Supplemental Table 2.

CD4 count recovery

On average, CD4 count increased from 391 (95% CI: 372–409) cells/mm^3 at the time of ART initiation, to 497 (95% CI: 478–515) cells/mm^3 after six months, and to 523 (95% CI: 495–551) cells/mm^3 after twelve months. We observed a decrease in the CD4 count in 20% of the women after six months and 18% of the women after twelve months. The median CD4 count measured during follow-up according to baseline CD4 category and type of ART is shown in Figures 2 and 3. The average CD4 gains after twelve
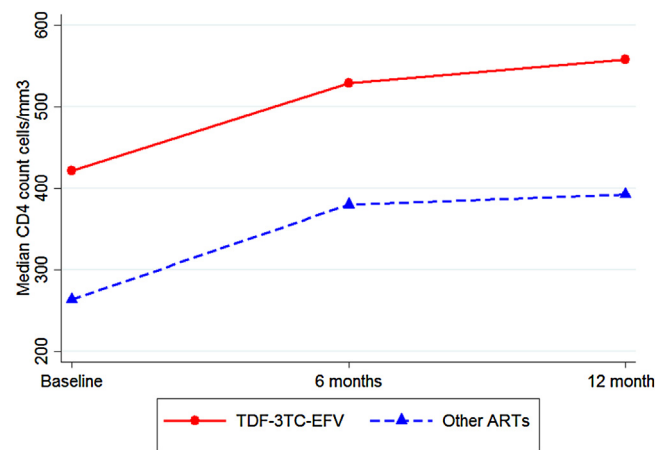
Figure 3. Median CD4 count during follow-up by type of ART regimen initiated in asymptomatic HIV infected pregnant women.
Legend: CD4 count measurement was available for 706 women at baseline, 668 after six months and 297 at twelve months. Of these, 569 women at the start of ART, 538 after six months and 130 after twelve months were on TDF-3TC-EFV.

months were 175 cells/mm^3 (SD = 187) among women with baseline CD4 below 350 cells/mm^3, 207 cells/mm^3 (SD = 162) among women with baseline CD4 between 350 and 499 cells/mm^3, and 6 cells/mm^3 (SD = 211) among women with baseline CD4 of 500 cells/mm^3 or more (p < 0.001). On average, CD4 count after twelve months reached 390, 624, and 698 cells/mm^3 for women with baseline CD4 counts below 350, 350 to 499 and 500 cells/mm^3 or more respectively. After twelve months of treatment, a CD4 count of above 500 cells/mm^3 was achieved by 22%, 75% and 82% of women with baseline CD4 below 350, 350 to 499 and 500 cells/mm^3 or more respectively.

We also evaluated CD4 normalization, which was defined as reaching CD4 count of 750 cells/mm^3 or more. CD4 normalization was achieved by 18% of women after twelve months. As compared to those with baseline CD4 count less than 500 cells/mm^3, a higher proportion of women with baseline CD4 count of 500 cells/mm^3 or more achieved CD4 normalization after twelve months (43.6% versus 8.6%, p < 0.001).

In adjusted regression analysis, treatment initiation at low level of CD4 count was associated with higher CD4 gains during follow-up. For example, compared to women with baseline CD4 count of 500 cells/mm^3 or more, those with baseline CD4 count between 350 and 499 cells/mm^3 had a larger CD4 gain after six (adjusted mean difference = 142 cells/mm^3, 95% CI: 101, 183) and twelve months (adjusted mean difference = 207 cells/mm^3, 95% CI: 140, 275) (Table 2). Compared to TDF-3TC-EFV, women who initiated other types of ARTs had lower CD4 gains after twelve months (adjusted mean difference = −80 cells/mm^3, 95% CI: −140, −21) (Table 2).

After adjusting for relevant covariates, we found that higher baseline CD4 count was positively associated with CD4 normalization following ART in these asymptomatic women. Compared to women with CD4 count of 500 cells/mm^3 or more at treatment initiation, a lower proportion of women with baseline CD4 count between 350 and 499 cells/mm^3 achieved CD4 normalization after six (adjusted OR = 0.10, 95% CI: 0.04–0.24) and twelve months (adjusted OR = 0.32, 95% CI: 0.13–0.76) (Table 3). We observed no strong evidence that the likelihood of CD4 normalization differed according to type of ART regimen (Table 3).

Clinical outcomes

A total of 706 pregnant women who contributed 682 person-years of follow-up were included in the analysis of clinical events.

Figure 2. Median CD4 count during follow-up by baseline CD4 count category in asymptomatic HIV infected pregnant women.
Legend: CD4 count measurement was available for 706 women at baseline, 668 after six months and 297 at twelve months. Of 706 women, 179 women had baseline CD4 500 cells/mm^3 and more, 137 women had baseline CD4 350–499 cells/mm^3 and 352 women had baseline CD4 less than 350 cells/mm^3.

Table 2

Association of baseline CD4 count and ART regimen with CD4 count gain from baseline to six and twelve months follow-up in asymptomatic HIV infected pregnant women.

Exposure variables	CD4 count gain (cells/mm^3) at six months (N = 668)				CD4 count gain (cells/mm^3) at 12 months (N = 297)			
	n	Mean (SD)	Unadjusted β(95%CI)	Adjusted β(95%CI)[a]	n	Mean (SD)	Unadjusted β(95%CI)	Adjusted β(95%CI)[a]
Baseline CD4 (cells/mm^3)								
≥500	179	−4.5 (224)	Reference	Reference	78	6 (211)	Reference	Reference
350–499	137	130 (152)	134 (97, 172)	142 (101, 183)	66	207 (162)	201 (139, 264)	207 (140, 275)
<350	352	158 (141)	162 (132, 193)	173 (139,208)	153	175 (187)	169 (118, 221)	200 (141, 259)
Type of ART								
TDF-3TC-EFV	538	106 (185)	Reference	Reference	235	144 (210)	Reference	Reference
Other ART types[b]	130	121 (174)	16 (−19, 51)	−29 (−65, 7)	62	111 (178)	−33 (−90, 24)	−80 (−140, −21)

ART: antiretroviral therapy, TDF-3TC-EFV: a combination of tenofovir, lamivudine and efavirenz.

[a] The regression analyses were adjusted for age at treatment initiation, gestational age at ART initiation, weight at treatment initiation, marital status, level of education, hemoglobin level and treatment adherence. In addition, baseline CD4 count and type of ART were adjusted for each other.

[b] Other type of ARTs include: ARTs comprised of TDF-3TC-NVP, ZDV-3TC-NVP or ZDV-3TC-EFV.

Table 3

Association of baseline CD4 count and type of ART regimen with CD4 normalization (CD4 ≥750 cells/mm^3) at six and twelve months in asymptomatic HIV infected pregnant women.

Exposures	CD4 normalization at six months (n = 668)			CD4 normalization at 12 months (n = 297)		
	n/N(%)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)[a]	n/N(%)	Unadjusted OR (95%CI)	Adjusted OR(95%CI)[a]
Baseline CD4 (cells/mm^3)						
>500	65/179 (36)	1	1	34/78 (44)	1	1
350–499	8/137 (6)	0.11 (0.05–0.24)	0.10 (0.04–0.24)	13/66 (20)	0.32 (0.15–0.67)	0.32 (0.13–0.76)
<350	9/352 (3)	0.05 (0.02–0.10)	0.06 (0.03–0.13)	6/153 (4)	0.05 (0.02–0.13)	0.06 (0.02–0.18)
Type of ART						
TDF-3TC-EFV	78/538 (15)	1	1	50/235 (21)	1	1
Other ART types[b]	4/130 (3)	0.19 (0.07–0.52)	0.43 (0.12–1.63)	3/62 (4.8)	0.19 (0.06–0.63)	0.48 (0.12–2.00)

OR: odds ratio, ART: antiretroviral therapy, TDF-3TC-EFV: a combination of tenofovir, lamivudine and efavirenz.

[a] The regression analyses were adjusted for age at ART initiation, gestational age at ART initiation, weight at ART initiation, marital status, level of education, hemoglobin level and treatment adherence. In addition, baseline CD4 count and type of ART were adjusted for each other.

[b] Other type of ARTs: include ARTs composed of TDF-3TC-NVP, ZDV-3TC-NVP or ZDV-3TC-EFV.

A total of 54 women were censored because treatment was interrupted for 3 or more months and one woman was censored after having died. During the follow-up, 24 women experienced HIV-related clinical events. Of these, 20 (2.9%) were WHO stage II, three (0.5%) were WHO stage III and one (0.2%) was WHO stage IV. Incidence rate of HIV-related clinical events was 3.5 per 100 person-years of follow-up (95% CI: 2.4–5.2 per 100 person-years). Incidence of HIV-related event was 5.3 per 100 person-years, among women with baseline CD4 count below 350 cells/mm^3; 2.2 per 100 person-years among women with baseline CD4 count between 350 and 499 cells/mm^3; and 1.1 per 100 person-years among women with CD4 count >500 cells/mm^3 (p = 0.01).

In adjusted analysis, the incidence of HIV-related clinical events among women with baseline CD4 of 500 cells/mm^3 or more was not significantly different from women with a baseline CD4 count between 350 and 499 cells/mm^3 (adjusted HR = 2.01, 95% CI: 0.35–12.55), or from women with a baseline CD4 count of less than 350 cells/mm^3 (adjusted HR = 4.10, 95%CI: 0.91–18.47) (Table 3). Similarly, the association between type of ART and incidence of clinical events observed in unadjusted analysis was attenuated in adjusted analysis (Table 4).

Discussion

Our findings indicated that starting ART for asymptomatic HIV-infected pregnant women before their CD4 count falls below 500 cells/mm^3 is beneficial for CD4 normalization (CD4 recovery to 750 cells/mm^3 or more) in resource-limited settings. Women who started ART at lower baseline CD4 count (<500 cells/mm^3) could not catch up with those who had higher baseline CD4 count (≥500 cells/

Table 4

Association of baseline CD4 count and type of ART with occurrence of HIV-related clinical events in asymptomatic HIV infected pregnant women who contributed 682 person-years.

Exposures	Person years of follow-up	Number of events	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Baseline CD4 (cells/mm^3)				
>500	184	2	1	1
350–499	141	3	1.95 (0.33–11.65)	2.01 (0.35–12.55)
<350	357	19	4.92 (1.15–21.12)	4.10 (0.91–18.47)
Type of ART				
TDF-3TC-EFV	553	14	1	1
Other ART types[b]	129	10	3.12 (1.39–7.03)	2.28 (0.94–5.51)

HR: hazard ratio, ART: antiretroviral therapy, TDF-3TC-EFV: a combination of tenofovir, lamivudine and efavirenz.

[a] The regression analyses were adjusted for age at treatment initiation, gestational age at ART initiation, weight at treatment initiation, marital status, level of education, hemoglobin level and treatment adherence. In addition, baseline CD4 count and type of ART were adjusted for each other.

[b] Other type of ARTs: include ARTs composed of TDF-3TC-NVP, ZDV-3TC-NVP or ZDV-3TC-EFV.

mm^3) after twelve months of treatment although the rate of CD4 gain was faster among women initiating ART at lower baseline CD4 count. It is well known that having a CD4 count within the normal range among HIV infected individuals is associated with lower risk of HIV-related illnesses (Le et al., 2013; Baker et al., 2008) and a greater life expectancy (May et al., 2014).

Although the benefit of early initiation of ART has been demonstrated by clinical trials (Group TAS, 2015; Group ISS, 2015), the benefit was not uniform across various patient groups. In addition, it is not certain that the observed effectiveness in clinical trials can be replicated in different real program settings in low income settings. Moreover, the types of ART regimens used in clinical trials were not common in low income settings which make generalization of the findings to these settings problematic. Therefore, observational studies demonstrating the benefit of early ART in real clinical settings are necessary. Our study showed that early initiation of ART may be beneficial in preserving or recovering immunity in resource limited settings. The finding ease the concerns that early ART may not be effective for asymptomatic adults with high level CD4 count and supports the recent recommendations of early initiation of ART for all HIV-infected individuals by the WHO (WHO, 2016). Previous studies also reported that initiating ART when the CD4 count is ≥500 cells/mm^3 compared to deferring treatment until the CD4 drops below 500 cells/mm^3 significantly increases the likelihood of CD4 normalization (Gras et al., 2007; García et al., 2004; Okulicz et al., 2015). The benefit of early initiation of treatment is further reinforced by previous findings which showed that early initiation of ART preserves immune function (Le et al., 2013).

On average CD4 count increased across all baselines CD4 categories during follow-up. However, the rate of CD4 count increase during follow-up was higher among women who initiated ART at a lower baseline CD4 count. The finding is not unexpected as most women who initiated treatment at higher baseline CD4 count already have normal or near normal CD4 count, and are therefore not expected to have large CD4 gains during follow-up. The likely CD4 count trajectory without treatment is a progressive decline after a transient increase during the acute HIV infection phase (Le et al., 2013). Preventing CD4 count decline is the likely benefit of treatment among women who have high baseline CD4 count. Previous studies reported inconsistent findings. Some studies reported a larger CD4 increase among patients with lower baseline CD4 count (Lifson et al., 2011; Sempa et al., 2013), and others demonstrated a similar rate of CD4 increase despite the difference in baseline CD4 count (Lawn et al., 2006; Lewden et al., 2007).

Our study could not determine the long term change in CD4 count, as the follow-up time was only twelve months. Findings from a few previous studies evaluating CD4 trajectories over time demonstrated that the CD4 counts continued to increase up to 3 to 4 years after initiation of ART before reaching a plateau after 4–5 years in all CD4 categories (García et al., 2004; Lifson et al., 2011). Other studies indicated that the CD4 counts continue to increase for 7 years among those who initiated treatment at CD4 count less than 350 cells/mm^3 (Gras et al., 2007; Sempa et al., 2013). However, these studies did not evaluate the effect of treatment initiation at different CD4 levels among asymptomatic HIV-infected individuals.

We also evaluated clinical outcomes according to baseline CD4 count. Outcomes such as AIDS defining illnesses and mortality during follow up period were very rare due to the short follow-up time. As a result, we considered WHO stage II–IV HIV-related clinical events in combination. The study demonstrated some evidence of lower risk of HIV-related clinical events among women who initiated ART at baseline CD4 count of ≥500 cells/mm^3 as compared to women who initiated treatment with a CD4 count below 500 cells/mm^3, although the confidence intervals were wide due to the small number of events.

The "90-90-90 treatment target" which aims at diagnosing 90% of HIV-infected individuals, treating 90% of those diagnosed and achieve viral suppression for 90% of treated individuals, is a key strategy to achieve one of the sustainable development goals (SDG) of ending AIDS as a public health threat by 2030 (UNAIDS, 2014). However, low level of treatment adherence, loss to follow-up, and drug resistance needs to be addressed to achieve the SDG goals. ART should be taken for life with adequate level of adherence to get the desired benefit. However, asymptomatic individuals with a high level of CD4 count might have poor adherence and be less motivated to continue treatment (Nachega et al., 2014). For example, a study in Malawi reported that 73% of women continued ART treatment three months after initiation but only 56% were adherent to treatment (Hauser et al., 2017). Drug resistance is another problem that should be taken into account. The 2017 WHO HIV drug resistance report showed that the level of HIV drug resistance among the first line drugs used in most low and middle income countries was very high; three of the four sub-Saharan African countries included in the report had greater than 10% pretreatment resistance for non-nucleoside reverse transcriptase inhibitors (NNRTIs) (ranging from 8.1% to 15.4%) (WHO, 2017). Mathematical modeling estimates showed that if NNRTI pretreatment resistance exceeds 10%, and NNRTI-based ART continue to be a first-line treatment in the next 15 years, NNRTI pretreatment resistance could become responsible for 16% of AIDS deaths (n = 890 000) and 9% of new HIV infections (n = 450 000) in sub-Saharan Africa alone (Phillips et al., 2017). Notably, early initiation of treatment is found to reduce the risk of HIV drug resistance compared to delaying treatment (Hamers et al., 2012; Fogel et al., 2016).

Our findings should be understood in the light of the following limitations. Because of the observational nature of the study, different confounding factors could bias the findings; but we were able to adjust for a broad range of known potential confounders. We also explore influence calendar year at the start of ART but we found no association between calendar year at the start of ART and treatment outcome. The study was conducted in resource limited urban settings which might limit its generalizability to other settings. Moreover, our study was limited by exclusion of a substantial number of women due to missing information, although our comparison of characteristics of those excluded and those included showed that the two groups were very similar. More women with lower CD4 counts were started on other ART types compared to TDF-3TC-EFV. This is because of evolution of the treatment guideline. Before 2013, efavirenz was not recommended during early pregnancy for fear of side effects; meanwhile eligibility for ART was based on CD4 count (<350 cell/mm^3) or disease progression. Viral load and CD4 to CD8 ratio which are important clinical indicators of treatment success were not measured. Our study was also limited by short follow-up period; as a result we could not evaluate the long term trend of CD4 count and clinical outcomes. Notably, previous studies indicated that most of the CD4 gains in patients on ART were achieved within one year of treatment (Lifson et al., 2011; Gezie, 2016).

In conclusion, initiation of ART for asymptomatic HIV-infected pregnant women with CD4 count ≥500 cells/mm^3 was beneficial to preserve or recover immunity after 12 months of treatment in resource limited settings. Our finding supports the recent WHO recommendations of universal ART for HIV-infected individuals including pregnant women as early as possible. A large-scale study on drug toxicity and drug resistance in resource-limited settings among men and women who initiate ART at different CD4 counts is warranted.

Conflicts of interest

We declare that we have no conflicts of interest.

Authors' contribution

YE, JHM, JS and MCM participated in designing the study. YE carried out data collection and first draft report preparation. YE, MCM, JHM, and JS have participated in data analysis, data interpretation and writing the manuscript. All authors contributed to edit the final report.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2019.02.019.

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