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Incidence and Risk Factors of Anemia among HIV/AIDS Patients Taking Anti-Retroviral Therapy at Tertiary Hospitals in Addis Ababa, Ethiopia: A Retrospective Cohort Study

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Abstract

Background
Anemia is a common problem in HIV infected patients. It can decrease the patient's functional capacity and quality of life. It is also commonly associated with faster disease progression and decreased survival. 52% of HIV infected patients in Addis Ababa suffer from anemia. Studies in Ethiopia so far focused on the general mortality associated with HIV infection and its associated factors. The main objective of this study was to determine the incidence rate and predictors of anemia among HIV/AIDS patients taking antiretroviral therapy.

Methods
A retrospective cohort study was conducted on patients aged 15 years and greater who were on ART at St. Paul's and ALERT hospital from January, 2008 to December, 2012. Survival analysis was conducted where the Kaplan Meier method was used to compare survivorship. Multivariate Cox regressions was also done to assess the significant predictors of anemia.

Results
A total of 616 patients on ART were followed for a median of 28 months (IQR = 10-34). Of these, 201 (33%) patients had developed anemia during the follow up time. The estimated survival (not developing anemia) at 12, 24 and 36 months were 72%, 42% and 29% respectively. The overall incidence of anemia was 35.3 per 100 person years. The independent predictors of incident anemia were age (AHR=1.017, 95%CI=1.0041 - 1.0307), chronic diarrhea (AHR=1.85,95%CI=1.3439-2.5695), baseline ART regimen (AHR=2.84, 95%CI=1.5224-5.3137), baseline CD4 count (AHR=4.96, 95%CI=3.4144 - 7.2049) and baseline ALT level (AHR=1.52, 95%CI=1.0335 - 2.2316).

Conclusion
The incidence of anemia was high in patients who were on Zidovudine therapy. CD4 count less than 200 cells per mm3 and Zidovudine containing ART regimen were the most important risk factors. Hence, it might be important to carefully look for these risk factors in order to prevent them or manage if they already exist in these patients. High incidence in patients on Zidovudine based regimen and older patients might support the value of assessing the level of hemoglobin regularly.

Background

There are various conditions that are associated with the advancement of HIV infection in to AIDS stage, usually when ART is not introduced at the appropriate time for the patients. One of them is Anemia. It is a condition in which an individuals' blood has a lower than the normal number of red blood cells. It can also occur when the red blood cells doesn't have enough amount of hemoglobin (Hgb). It is an important clinical problem in patients with HIV infection and those with AIDS. It can have serious implications, which may vary from functional and quality of life decrements to an association with disease progression and decreased survival [1].

Based on recent estimates from the World Health Organization (WHO), the prevalence of anemia is 24.8% globally [2]. It affects an estimated 2 billion people worldwide [2]. It is the most common hematologic abnormality associated with HIV infection. Although the burden of anemia in HIV/AIDS patients is not very well understood, it is estimated that about 60 to 80% of patients in their late-stage of the disease are affected worldwide [3]. In these patients, 22% of anemia is thought to be caused by the several treatments given to the patients including the antiretroviral medications [3,4]. In asymptomatic patients i.e. patients without apparent clinical manifestation of the disease, it is also estimated that the prevalence of anemia could reach up to 30%. When we look at the global prevalence of anemia in HIV infected patients with regard to sex, females are disproportionately more affected by the condition as compared to males. In a study conducted in the US, it was reported that women had 71% greater prevalence of anemia than men when anemia is defined as hemoglobin (Hgb) of less than 12 g/dl in women and Hgb less than 13 g/dl in men [3].

A comprehensive figure for the burden of anemia in HIV/AIDS patients in the Sub Saharan Africa probably hasn't been estimated. But, there are several studies conducted in individual countries in the Sub Saharan Africa to estimate the prevalence of anemia in HIV infected population. According to the report of Egyptian Demographic and Health Survey in 2010, it was estimated that 47% of the general population had prevalent anemia while, its prevalence goes up to 54% in the HIV infected population [5]. In Nigeria it was also estimated that about 60.6% of the HIV infected population suffer from anemia [6]. In Addis Ababa, an estimated 52.6% of the HIV infected population has prevalent anemia [7]. Another estimate also suggests that hematologic abnormalities like neutropenia, thrombocytopenia and anemia are very common in HIV patients who are taking ART in Addis Ababa [8]. In this study, it was also shown that about 43.3% of female patients and 43.2% of male patients were anemic [8].

The survival rate of HIV/AIDS patients on highly active antiretroviral therapy and risk factors of mortality in these patients have been very well understood in the developed world. But, the incidence, anemia free survival time, and its risk factors among HIV/AIDS patients on HAART has not been very well understood in resource poor settings like Ethiopia, although there are a few prevalence studies conducted at different parts of the country. Therefore, the main aim of this study is to describe the incidence of anemia in HIV infected patients who are taking HAART and the associated factors.

Methods and Materials

This study was conducted in St. Paul's and ALERT hospital which are located in Addis Ababa. The hospitals started providing a comprehensive antiretroviral treatment since 2005. All HIV/AIDS patients aged greater than or equal to 15 years who were taking ART in the two hospitals from January, 2008 to December, 2012 were the study population. The patients were either on Zidovudine or Non Zidovudine based regimen. In the Ethiopian ART guideline, Zidovudine based regimens are the first line ART regimens. However, patients are assigned to Stavudine or Tenofovir based regimens whenever they have contraindications to start Zidovudine based regimens.

A retrospective cohort study design was employed on a sample of 616 patients from the two hospitals to assess the incidence and risk factors of anemia in the study population. A unique identification number was assigned for each of the patients in the ART registers and table of random numbers was used to take the samples. Patients who already had anemia at baseline or before the start of the cohort period, patients with incomplete recording at base line and follow up, transfer in patients and patients who were pregnant during the cohort period in the two hospitals were excluded from this study.

Before collection of the data, a data extraction tool was prepared and pre tested. Additionally, the nurses who were selected to collect the data were given one day training on the data extraction tool and how to collect data from registers to ensure no selection or information bias was introduced at the time of data collection. During the data collection time, the principal investigator was also around in the hospitals in order to supervise the data collectors. Finally, after data collection, all the tools were examined for accuracy and completeness.

STATA version 11 (STATA Corporation, College Station, Texas 77845 USA) was the statistical software that was used for most of the statistical analyses in this study. Descriptive statistics such as frequencies, percentages, median, and interquartile ranges were used to describe the study population in relation to relevant background, clinical and laboratory variables. To compare the survivor ship of different categories of patients, Kaplan-Meier curves and log rank test was used while multivariate cox regression was used to identify the independent predictors of anemia.

Permission to undertake the study was obtained from the Research and Community Service Office of Mekelle University, Collage of Health Sciences. Official letter of cooperation was written from Federal ministry of Health to concerned bodies in the hospitals where the data collection took place. Additionally, further ethical clearance was obtained from ALERT hospital Armor Hansen Research Institute ethical review committee and St. Paul's hospital ethical review committee.

Confidentiality of the patient's information was strict and no information was handed over to a third party.

Results

Baseline characteristics

A total of 616 HIV/AIDS patients who were taking antiretroviral therapy in St. Paul's and ALERT hospital were included in to the study of whom 201 (33%) had developed anemia while 415 (67%) were censored. Of the censored patients, 341 (55%) didn't develop anemia until the end of the study, 45 (7%) were drop outs and 29(5%) were lost to follow up. They were followed for a median of 28 months (IQR= 10-34 months). Majority of the patients, 374 (61%) had developed some type of opportunistic infection in the past out of whom 157 (51%) were on non Zidovudine regimen while 217 (70.5%) were on Zidovudine based regimen. Among all the patients, 166 (27%) of them had past tuberculosis infection, but only 157 patients were treated for the disease in the past while the rest didn't. Furthermore, 135 (22%) patients had either oral or vaginal Candidiasis whereas 93 (15%) had chronic diarrhea in the past. Among those who had oral or vaginal Candidiasis, 50 (16.2%) were on non Zidovudine regimen while 85(27.6%) were on Zidovudine regimen. (Table 1 and 2).

Variables		"Non Zidovudine (N=308) [n (%)] "	"Zidovudine (N=308) [n (%)] "
Sex	Male	107 (34.74)	108 (34.09)
	Female	201 (65.26)	200 (64.94)
Educational	No education	80 (25.97)	78(25.32)
status	Primary education	159 (51.62)	193 (62.66)
	Secondary education	39 (12.66)	19(6.17)
	Tertiary education	30 (9.74)	18(5.84)
Employment	Non employed	120 (38.96)	97(31.49)
	Employed	188 (61.04)	211(68.51)
Place of	Rural	112(36.36)	102(33.22)
residence	Urban	196(63.64)	205(66.78)
Anemia	Censored	234 (75.97)	181(58.77)
	Anemia	74(24.03)	127(41.23)
Opportunistic	No	151(49.03)	91(29.55)
infection	Yes	157(50.97)	217(70.45)
Tuberculosis	No	237(76.95)	213(69.16)
infection	Yes	71(23.05)	95(30.84)
Age	Age range	16 – 68 years	17 – 71 years
"Baseline CD4 Count"	Count range	85 – 340 cells/mm3	50 – 295 cells/mm3

Table 1:- Baseline Socio-demographic and clinical characteristics of patients who were taking ART in St. Paul's and ALERT hospital during January 2008 – December 2012 (n=616)

Incidence and anemia free survival time

The overall incidence of anemia was 35.3 per 100 person years (95% CI= 0.307 - 0.405). It was higher in patients who were taking Zidovudine containing regimen which is 44.5 per 100 person years (95% CI = 0.374 - 0.529) as compared to those patients who were taking non Zidovudine containing regimen which is 26.01 per 100 person years (95% CI = 0.207 - 0.327. The highest incidence was observed after 3 years of follow up in both categories.

The overall median survival time of the patients for developing anemia was 23 months while it was 17 months in those patients who were on Zidovudine regimen (IQR=11-26). Furthermore, the estimated probability of survival (not developing anemia) at 12, 24 and 36 months are 72%, 42 % and 29 % respectively.

Variables		"Non Zidovudine (N=308) [n (%)] "	"Zidovudine (N=308) [n (%)] "
Oral or vaginal	No	258(83.77)	223(72.40)
Candidiasis			
	Yes	50(16.23)	85(27.60)
Chronic	No	274(88.96)	249(80.84)
Diarrhea			
	Yes	34(11.04)	59(19.16)
Tuberculosis	No	246(79.87)	213(69.16)
treatment			
	Yes	62(20.13)	95(30.84)
Baseline	Greater than or equal to 60	60(19.48)	57(18.51)
Weight	Kg		
	Less than 60 Kg	248(80.52)	251 (81.49)
Baseline	Working	53(17.21)	54 (17.53)
functional			
status	Ambulatory	233(75.65)	237 (76.95)
	Bed ridden	22(7.14)	17 (5.52)
CD4 count	Greater than or equal to 200	51(67.86)	106 (68.51)
	cells		
	Less than 200 cells	257(32.14)	202 (31.49)
Baseline ALT	Normal	281(91.23)	238 (77.27)
	Abnormal	27(8.77)	70 (22.73)
Baseline AST	Normal	208(67.53)	197 (63.96)
	Abnormal	100(32.47)	111 (36.04)

Table 2:- Baseline clinical and laboratory characteristics of patients who were taking ART in St. Paul's and ALERT hospital during January 2008 – December 2012 (n=616)

Predictors of anemia

In bivariate analysis, for a 1 year increase in age there was a 1.4% higher risk of anemia (UHR=1.014, 95% CI=1.0006 - 1.0267) but after controlling for the other variables1, the risk increased to 1.7 % for an increase in 1 year of age (AHR=1.017, 95% CI=1.004 - 1.0307). Chronic diarrhea was also found to be a significant predictor of incident anemia in this study. Patients who had chronic diarrhea in the past had 2.08 higher risk of anemia than patients without history of chronic diarrhea (UHR=2.08, 95% CI=1.5167 – 2.8659). At the multivariate analysis, the risk of developing anemia in patients with history of chronic diarrhea decreased to 1.85 (85%) relative to those patients without chronic diarrhea (AHR=1.85, 95% CI=1.3439 - 2.5695) after controlling for the other variables2. Patients who were on Zidovudine based regimen at baseline had 71% higher risk of anemia than those patients who were on non Zidovudine based regimens (UHR=1.71, 95% CI=1.2838 - 2.2776). After adjusting for the rest of the variables 3in the multivariate model, the risk even became higher (AHR=2.84, 95% CI=1.5224 - 5.3137).

Patients with CD4 count less than 200 cells per cubic millimeter had 5.91 higher risk of developing anemia as compared to patients who had greater than or equal to 200 cells per cubic millimeter (UHR=5.91, 95% CI=4.3346 - 8.0501). After adjusting for other variables4 in the multivariate model, the

risk was lowered to 4.96 (AHR=4.96, 95% CI=3.4144 - 7.2049). Patients who had abnormal ALT level had 38% higher risk of anemia than patients with normal values but it was not a statistically significant association (UHR=1.38, 95% CI=0.9601 - 1.9802). But, at the multivariate level, after controlling for other variables5, ALT had a statistically significant association with anemia where patients with abnormal ALT values had 52% higher risk of anemia as compared to patients with normal ALT values (AHR=1.52, 95% CI=1.0335 - 2.2316). Table 3 shows the crude and adjusted hazard ratios of the variables with their 95% confidence intervals.

Variables		UHR [95% CI]	P-value	AHR [95% CI]	P-value
Sex	Male	1			
	Female	1.44 [1.0663- 1.9482]	0.002	--	
Age		1.014 [1.0006 - 1.0267]	0.004	1.017 [1.0041 - 1.0307]	0.011
Oral or	No	1			
vaginal	Yes	1.74 [1.2969 - 2.3235]	0.001	--	--
Candidiasis					
Chronic	No	1		1	
Diarrhea					
	Yes	2.08 [1.5167 - 2.8659]	0.001	1.85 [1.3439 - 2.5695]	0.001
Baseline	Non ZDV regimen	1		1	
ART	ZDV regimen	1.71 [1.2838 - 2.2776]	0.001	2.84 [1.5224 - 5.3137]	0.001
regimen					
Baseline	Working	1	--	1	--
functional					
status	Ambulatory	0.71 [0.5038 - 0.9973]	0.048	0.67 [0.4783 - 0.9597]	0.028
	Bed ridden	0.57 [0.2931 - 1.1068]	0.097	0.47 [0.2407 - 0.9228]	0.028
Baseline	Stage I	1	--		
WHO	Stage II	0.98 [0.6443 - 1.4762]	0.906		
staging					
	Stage III	1.95 [1.1926 - 3.2068]	0.008	--	--
	Stage IV	1.65 [0.9608 - 2.8337]	0.007		
Baseline	>= 200 cell	1		1	
CD4 count			0.001		0.001
	< 200 cells	5.91 [4.3346 - 8.0501]		4.96 [3.4144 - 7.2049]	

Table 3:- Shows the unadjusted and adjusted hazard ratios of socio demographic, clinical and laboratory variables

Discussion

Based on the results of this study, the overall incidence of anemia in both categories was 35.3 per 100 person years. When seen separately, the overall incidence was higher in patients who were taking Zidovudine containing regimen (44.5 per 100 person years) as compared to patients who were on non Zidovudine based regimen (26.01 per 100 person years). Within just 6 months of follow up period, the incidence of anemia was 40.6 and 22.8 per 100 person years in patients taking Zidovudine and non Zidovudine regimens respectively. After two years of follow up, the incidence had increased to 67.3 and 51.4 per 100 person years in the two categories respectively.

Several other studies favor the results of this study with regard to the incidence of anemia. In a study conducted in Uganda, HIV infected patients who had no anemia at enrollment were followed for development of anemia and the incidence rate was found to be 259/1000 person years [9].In another study conducted in eastern India, Zidovudine induced anemia was found in HIV infected patients taking ART with a cumulative incidence of 16.2% [10]. This study also reported that the incidence of anemia was higher in the first 6 months of follow up [10].A study conducted in the US by Crukendall et al to describe the incidence of anemia in HIV infected patients who were treated with ART, had found that the incidence of anemia was 24.6 and 8.1 per 100 person years in Zidovudine and non Zidovudine cohorts after 6 months of follow up [11]. They had also proved that the incidence was higher in Zidovu-

dine cohorts than non Zidovudine cohorts, which is also consistent with the current study [11]. However, in their study the incidence was highest with in the 6 months of follow up [11] as opposed to the current study where the highest incidence was found after three years of follow up. The current study is also in line with another research conducted in the US by Sullivan and his colleagues to study the incidence, associated risk factors and the effect on survival of anemia in HIV infected persons [12]. In this study, it was found that the overall 1 year incidence of anemia was 36.9 per 100 person years for patients with AIDS defining illness and 12.1 per 100 person years for patients with CD4 count less than 200 cells mm3[12].

The difference in the time for peak incidence between the current study and the other literatures mentioned above might be due to the fact that some of them had studied pregnant women and pediatric patients where such patients could develop anemia within a short period of time and some of the studies had a short period of follow up unlike the current study which is about 4 years.

In the current study, age was found to be an independent predictor of anemia. At the bivariate level of analysis, for a 1 year increase in age there was a 1.4% higher risk of anemia but after controlling for the effect of other variables6, the risk has increased to 1.7% for an increase in 1 year (AHR=1.017, 95% CI=1.004 - 1.0307). In a study which was done by Crukendall and his colleagues, age was a significant predictor of anemia as well [11]. In their study, an increment in age by 1 year had a protective effect against anemia (HR=0.998, 95% CI= 0.978–1.017) but in the current study an increase in age by 1 year had an increased risk of anemia [11]. In a study conducted in Iran by Ramezani and his colleagues, they found no statistically significant association between age and incident anemia both at bivariate and multivariate levels of analysis as opposed to the results of the current study but the lack of association in their study could be due to inappropriate categorization of age [13]. A study by Semba and his colleagues reported that for a 5 year increase in age, there was a 12% higher risk of developing anemia in patients who were taking ART which quietly resembles the current study [14]. In another study conducted in the US on the incidence of anemia by A. A Butt and his colleagues, it was found that an age category of greater than 40 years was associated with an incident anemia at multivariate level of analysis (HR=4.31, 95% CI=1.70–10.91) which is consistent with the current study [15].

Chronic diarrhea was also found as a significant predictor of incident anemia in this study. Patients who had chronic diarrhea in the past had 2.08 higher risk of anemia than patients without history of chronic diarrhea. At the multivariate level, the risk of developing anemia in patients with history of chronic diarrhea decreased to 1.85 (85%) relative to those patients without chronic diarrhea (AHR=1.85, 95% CI=1.3439 - 2.5695) after controlling for the other variables7.Although no studies have been found that had reported the association of chronic diarrhea with development of anemia during literature search, clinically it is proven that patients with chronic diarrhea have mal- absorption of nutrients including the micronutrients [16]. Iron is one of the micronutrients which will be poorly absorbed in such patients leading to iron deficiency anemia [16]. In some cases, patients who have chronic bloody diarrhea also suffer from anemia [16]. But, unlike the incident anemia due to Zidovudine, anemia due to chronic diarrhea takes a longer time to develop. In the case of Zidovudine toxicity, incident anemia is seen as quickly as 3 to 6 months [16].

Several previous studies had found that the use of Zidovudine as independent significant predictor of incident anemia in HIV patients [17,12,11,10] and the current study further confirms this except that the time of incidence was a bit longer in the current study. In this study, patients who were on Zidovudine based regimen at baseline had 71% higher risk of anemia than those patients who were on non Zidovudine based regimens. After adjusting for the rest of the variables 8in the multivariate model, the risk even became higher (AHR=2.84, 95% CI=1.5224 - 5.3137). Crukendall and his colleagues had found that Zidovudine as a significant predictor of anemia at multivariate level (HR=1.6, P=0.005). In the study by Sullivan et al, prescription of Zidovudine had a higher risk of anemia in HIV infected patient (HR=1.5, 95% CI=1.1 – 2). The current study is also consistent with a study conducted in eastern India by Agarwal et al where high incidence of Zidovudine induced anemia was reported [10]. Another study in Iran is also in similar with the current study in that Zidovudine was a statistically significant predictor of anemia [18]. Butt and his colleagues in their study about the incidence of anemia in HIV infected patients had reported that use of Zidovudine was significantly associated with incident anemia (HR=2.5, 95% CI= 1.2 – 3.4) [15]. Several other studies have also found the association between Zidovudine use and development of anemia [7,17,12,14]. Some studies report that the use of HAART in general is associated with resolution anemia rather than development of incident anemia irrespective of the use of Zidovudine. Usually, Zidovudine treatment is associated with suppression of bone marrow and other hematopoietic activities in general leading to low production of the red blood cells and other types of blood cells in the bone marrow [12,19].

CD4 count was also another significant predictor of anemia in this study. Patients with CD4 count less than 200 cells per cubic millimeter had 5.91 higher risk of developing anemia as compared to patients who had at least 200 cells per cubic millimeter. In the multivariate model, the risk was lowered to 4.96 (AHR=4.96, 95% CI=3.4144 - 7.2049) in the presence of other risk factors9. Furthermore, the median survival time of the patients who had CD4 count less than 200 cells per mm3 was just 12 months as compared to 17 months for Zidovudine use, which is very shorter. Several literatures confirm this association [12,14,20,21,11]. In the study of Crukendall et al, CD4 counts less than 200 cells had 3 times higher risk of anemia than patients with CD4 counts of greater than 200 cells per cubic millimeters (HR=2.99, 95% CI= 2.119–4.138) [11]. In a study of Sullivan and his colleagues, patients with CD4 counts less than 200 cells per cubic millimeter, had 5 times more risk of developing anemia than patients with higher CD4 counts (HR=5.0, P=4.0- 6.2) [14]. A study by Berhane K et al, also confirms the association but with lower risk than the current study [21]. Another study by M. Marin and his colleagues in Mexico, reports that lower CD4 counts are associated with

increased risk of anemia even after controlling for the other risk factors like use of Zidovudine [20]. A study by Semba and his colleagues reported CD4 counts below 200 cells per cubic millimeter had 68% higher risk of anemia than patients with higher counts of CD4 cells [14]. But, the study of Ramezani and his colleagues which was conducted in Iran had found no association between CD4 count and development of anemia opposing the result of this study [18]. But the reason for no association in this study might be due to the fact that the study was more of prevalence than incidence study.

Another predictor found significant in this study is the baseline ALT (Alanine aminotransferase) level. At the multivariate level of analysis, patients with abnormal ALT values had 52% higher risk of anemia as compared to patients with normal ALT values after controlling for other variables 10(AHR=1.52, 95% CI=1.0335 - 2.2316). Once again this variable is not mentioned as a predictor of anemia in the literatures used in this study and was not found as far as the literature was searched. But, biologically there are evidences which support this finding. It is known that the liver stores iron and processes hemoglobin for use of its iron content making it one of the important organs in the hematopoietic system [16]. When there is an insult to the liver, the body will be unable to store iron and the iron in hemoglobin will not be processed so that it will be used in the production of red blood cells which leads to anemia [16]. Alanine aminotransferase (ALT) is an enzyme which is produced by liver and is involved in a number of metabolic activities. It is used by clinicians as a primary indicator of liver functions as its production is deranged during liver injury [3,16]. Therefore, abnormal levels of ALT could indicate a disturbance in the functioning of liver which could have its own implication to the hematopoietic system including decreased production of RBCs (anemia) [3,16]. In a similar manner, baseline functional status of the patients was also another statistically significant predictor of anemia.

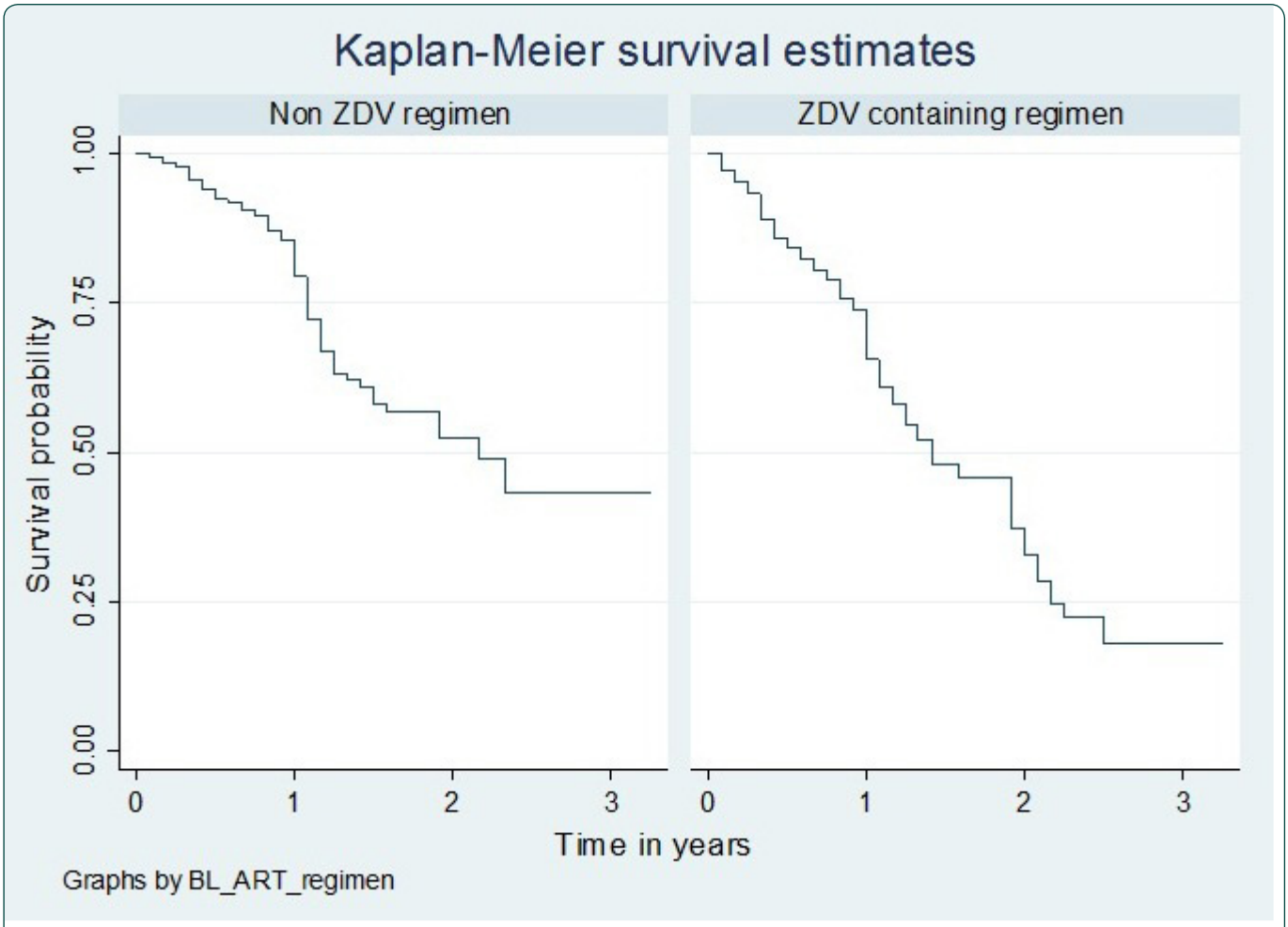

Figure 1. Kaplan Meier survival function by baseline ART regimen

Conclusion

In conclusion, the overall incidence rate of anemia (35.3 per 100 person years) was high in the cohort of patients in the two hospitals (St. Paul's and ALERT hospital) and their median survival time (23 months) was longer as compared to most of the cohorts in other studies. The excess incidence rate of anemia attributable to exposure to Zidovudine was 18.4 per 100 person years and 80 cases of anemia could have been averted if patients were not exposed to Zidovudine or were put to other kinds of regimens. Age of the patients, past history of chronic diarrhea, baseline ART regimen, baseline CD4 count and baseline ALT level are the independent predictors of incident anemia in the cohort of patients at the two hospitals.

None of the socio-demographic variables were significant predictors of anemia at the multivariate model except age.

Competing interests

The authors declare that they have no competing interests.

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