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Full Length Research Paper

Current status of human immunodeficiency virus and hepatitis C virus (HIV/HCV) co-infection in Cameroon: Sero-prevalence, risk factors and correlation with markers of liver function and CD4 cells rate in patients diagnosed in three hospital settings

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This study investigates the current status of HIV/HCV co-infection through viral sero-prevalence and correlation with liver markers and CD4 count in three hospital settings in Cameroon. Blood samples of 75 newly diagnosed HIV patients, and 546 people attending the target hospitals were screened for HCV(antigen-antibodies) using enzyme-immunoassay. Biochemical liver markers (ALT-AST-γ-GT-Bilirubin) and CD4-cell count were also analyzed. Statistical analysis was performed using student's t-test, χ2-test and Pearson correlation. The statistical significance was set at the threshold p≤0.05. Out of 75 people with HIV, 10(13.33%) were diagnosed with HIV/HCV co-infection; 56(10.25%) individuals from the cohort of 546 participants were diagnosed with HCV infection and 5(8.93%) were confirmed HIV positive. Results showed that HCV infection rate is higher among HIV patients than among the general population. For the two populations, co-infection rate was higher in women: 7(9.3%) and 3(4%) respectively in HIV positive patients, 3(5.35%) and 2(3.57%) in HCV patients. Women comprised the majority of people with HIV (72%) while men were the majority in the HCV-infected population (78.57%). Mean age in co-infected individuals was higher, with 93.33% aged 50 years or above. A negative and significant correlation was associated with CD4 count, ALT activity and bilirubin concentration in people with HIV, whereas in HIV/HCV co-infected patients, positive and significant correlations were associated with ALT, AST and γ-GT. HIV/HCV co-infection is a concern in hospital settings in Cameroon. HCV screening should be compulsory for patients and integrated in the existing guidelines/policies in Cameroon.

Key words: Seroprevalence, HIV/HCV, co-infection, risk factor, correlation, disease stage.

INTRODUCTION

Human immunodeficiency virus/hepatitis C virus (HIV/HCV) co-infection is becoming an important factor of co-morbidity and mortality, but many settings in sub-Saharan Africa still face disease unawareness even in

hospital surroundings. Viral infections are among the most serious worldwide public health problems, affecting millions of people worldwide. Sub-Saharan Africa that represents only 13% of the world population is the hardest hit region by these infections, home to nearly 70% of people living with human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) (PLHIV).In 2015, there were 36.7 million people living with HIV, including 2.1 million new infections. Western and Central Africa are home to 18% (6.5 million) of these infections, right after the Eastern and Southern Africa, 52% (19.0 million) and before Asia and the Pacific, 14% (5.1 million) (UNAIDS, 2016). Cameroon remains in a situation of high incidence for HIV, with a seroprevalence of 4.3% in adults aged 15 to 49 years (National Institute of Statistics, 2011).

The global response to the HIV/AIDS epidemic has improved human health: the effectiveness of highly active antiretroviral therapy (HAART) in improving the quality and lifespan of HIV patients has revolutionized the field of HIV care. However, co-infections with viruses like hepatitis B (HBV) and hepatitis C (HCV) appear to compromise the benefits of efficient antiretroviral drugs by increasing the morbidity and mortality in HIV-infected populations. Chronic hepatitis C has been reported as major cause of liver diseases in HIV infected people (Soriano et al., 2011). It is now well known that HIV/HCV co-infected patients are three times more likely to develop complications than those who are HIV mono-infected (Kim et al., 2005).

The introduction of direct acting antivirals (DAAs) like “Daclatasvir”, “Simeprevir” and “Sofosbuvir” against HCV is revolutionizing the field of HCV care as HAART did in 1996 with HIV, and therefore improving the prognosis of co-infection. However, due to their cost, DAAs are unavailable to the vast majority of patients in sub-Saharan African countries. Furthermore, whether available HCV therapeutics are equally efficacious on HCV strains circulating in sub-Sahara Africa has not been investigated. Therefore, affordable and widely accessible means to control and eradicate HCV infection worldwide are still needed. An important hallmark of HIV/HCV co-infection is that many people living with HIV in sub-Saharan Africa do not know their HCV status, since HCV screening tests are not yet as systematically performed as HIV screening tests, even in so-called “Reference Hospitals”. In addition, screening tests, when they do exist for HCV serology, are often based on rapid diagnostic tests, while immunoenzymatic ultra-tests are available for HIV health care, and directly integrated in the management policies.

In Cameroon, the plan to tackle HIV infection is well established: reduce the morbidity and mortality through the various prevention strategies of new infections, and the use of HAART organized in 1st, 2nd and 3rd lines of treatment provided to patients (Mbanya et al., 2008; Cameroon National AIDS Control Committee, 2010; Cameroon 2014 Country Operational Plan, 2014).

Conversely, the management plan for HCV infection is still in progress, without any written plan available to date (WHO, 2013). Research findings that provide policy makers with accurate support to improve the existing management policies are still sparse in Cameroon. Previous studies attempted to investigate the epidemiology of HCV infection either in sentinel surveillance conditions (e.g. pregnant women, maintenance haemodialysis, patients attending health facilities for care), or among first time blood donors (Halle et al., 2009; Noubiap et al., 2013; Noubiap et al., 2015; Luma et al., 2016a; Ankouane et al., 2016).

Very few studies have addressed and/or focused on the HIV/HCV co-infection and the impact on the disease progression. More accurate and reliable data among which co-infection sero-prevalence and risk factors studies, are still needed as prerequisite to the investigation of the disease progression in sub-Saharan Africa, vaccine and drug development strategies worldwide.

The aim of this study was to determine the sero-prevalence of HIV/HCV co-infection in various populations using the ultra immunoassay, as well as scrutinising the correlation with markers of liver function and CD4 count rate in Yaoundé, Cameroon.

METHODOLOGY

Study design, period and setting

The present study was a cross-sectional study based on biological and sociodemographic data. Information/sensitization and sample collection were done from November 2015 to February 2016, and between June TO October 2016 in three hospital settings in Yaoundé, Cameroon: Yaoundé Central Hospital, Yaoundé Military Hospital and “Clinique Bastos”.

Yaoundé Central Hospital

Yaoundé Central Hospital is a 381 bed tertiary level teaching hospital. The hospital employs about 800 staff including 95 doctors and about 270 nurses. The hospital provides surgical care, obstetrics, gynaecology and elderly care services along with radiology, intensive care, emergency services and an outpatient clinic to the population of the city and more widely across the country. The hospital is also a reference research and surveillance

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centre. It has an outpatient daily clinic for HIV/AIDS management.

Military Hospital

The military hospital in Cameroon's capital, Yaoundé, provides health care to Cameroonian and Chadian troops of the regional force, as well as to civil citizens. The hospital has a capacity of 200 beds. It is a treatment centre for HIV/AIDS, with laboratory equipped for HIV, HBV, HCV testing, confirmation and biochemical blood tests for patient's monitoring. The hospital receives the majority of HIV positive cases in the military, one of the key populations in Cameroon.

"Clinique Bastos"

"Clinique Bastos" is a private hospital for both in and out-patients care, with a capacity of about 25 beds. It mostly receives Cameroonians of the middle and upper economic classes. All the three hospital settings are authorized treatment facilities for people living with HIV/AIDS in Cameroon (PLHIV). It is important to mention that the majority of PLHIV in these health facilities, as in other health facilities in Cameroon do not know their status for HBV and/or HCV infection.

Target population/study participants

The study population consisted of patients attending the hospitals for consultation, and specialized centres within the aforementioned hospitals (for example, Day Care Hospital (where people living with HIV/AIDS are observed, and also receive health care) as well as Hepato-gastroenterology centre). HIV-positive patients were first recruited in Yaoundé Central Hospital, whereas another cohort of participants were further enrolled and screened for hepatitis C virus in the three health facilities. According to the Demographic and Health Survey and Multiple Indicators Cluster Survey (DHS-MICS), the HIV seroprevalence in Cameroon is higher (4.3%) compared to the HCV seroprevalence, 1.03% in the general population. Therefore, a high sample size should be considered while screening the general population for HCV infection.

Study inclusion criteria

Participants in the present study were those who had never been screened for HCV infection. Participants were fairly selected irrespective of gender, ethnicity, tribe, or religious belief. Enrolled participants were patients who agreed to sign a consent form after being informed of the nature of the study, the potential benefits and minimal foreseeable risks associated with the sample collection, as well as the voluntary nature of the participation.

Data collection procedure and analyses

Socio-demographic information and other relevant possible risk factors for the study participants (age, marital status, level of education, occupation) were collected using a questionnaire with both closed and open questions. About 4 mL of venous blood was collected by venous puncture in tube with EDTA. Blood specimens were centrifuged at 1,500 rpm for 5 minutes; 1mL plasma aliquots were made and separately stored at -20°C and -80°C for subsequent analyses (a total of 2 aliquots per sample). An aliquot (plasma) stored at -20°C was used for the HCV screening test.

Principle of detection of HCV infection

All plasma samples (from PLHIV and the other cohort of participants) were screened for HCV using Monolisa HCV Ag-Ab ULTRA assay (BioRad, France). Monolisa HCV Ag-Ab ULTRA assay is an enzyme immunoassay for the detection of HCV infection, based on the detection of capsid antigen and antibodies associated with an infection by Hepatitis C virus in patient serum or plasma. The microplate solid phase is coated with monoclonal antibodies against capsid protein of Hepatitis C virus, two recombinant proteins produced by E. coli from NS3 region: genotype 1 and 3a, one recombinant antigen from the non-structural region NS4, and a mutated peptide from the capsid of structural area of the hepatitis C virus genome. The conjugates used are: mouse biotinylated monoclonal antibodies against the hepatitis C capsid that do not react against the hepatitis C capsid mutated peptide coated on the microplate; mouse peroxidase-labelled antibodies to human IgG and peroxidase-labelled streptavidin.

Biochemical parameters

Biochemical markers of liver function (serum activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline phosphatase (ALP), and serum concentration of conjugated bilirubin), as well as CD4 T-cells count were collected and analyzed.

Data preparation, management and analysis

The effect size for this study was computed using G*Power version 3.1.9.2 software, with post-hoc power analysis. Data obtained were subsequently entered, cleaned and analyzed using the Statistical Package for Social Sciences (SPSS) software (version 22.1). Mean, frequencies and percentages were used to summarize descriptive statistics of the data. Chi-square (X2) test was used to assess relationships between selected and/or qualitative variables namely gender, sex, marital status, level of education and occupation. Pearson correlation was used to determine the relationship between the biochemical parameters and CD4 cells count. The significant difference was set at the threshold $p \leq 0.05$.

RESULTS

The effect size for this study was computed using G*Power version 3.1.9.2 software (Faul et al., 2007; Faul et al., 2009), with post-hoc as type of power analysis. The sample size (N=75) was in conformity with the effect size, 0.3 with X2 test, and 0.6 with the Pearson correlation. In the present study, 75 newly diagnosed people with HIV (PLHIV) in Yaoundé Central Hospital, as well as a cohort of 546 patients attending Yaoundé Central hospital, Military Hospital and Clinique Bastos were enrolled.

Sex and age variables

Out of 75 PLHIV enrolled, 54 (72%) were women and 21 (28%) were men (Table 1), whereas among the 56 HCV infected people from the cohort of 546 individuals, 12 (21.43%) were female and 44 (78.57%) were male (Table

Table 1. Distribution of the 75 people living with HIV in Yaoundé Central Hospital within age groups and sex (November 2015 to February 2016).

Age group (years)	Female (%)	Male (%)	Total (%)
21 – 30	5 (6.7)	1 (1.3)	6 (8.0)
31 – 40	6 (8.0)	1 (1.3)	7 (9.3)
41 – 50	12 (16.0)	7 (9.3)	19 (25.3)
>50	31 (41.3)	12 (16.0)	43 (57.3)
Total	54 (72.0)	21(28.0)	75 (100)
Mean age	50.41±11.67	52.38±10.24	50.96±11.26

Table 2. Distribution of individuals tested HCV positive among 546 participants in the three health facilities in Yaoundé (June to October 2016).

Health facility	Total tested	Total tested positive (%)	Prevalence (%)	Female (%)	Male (%)
Yaoundé Central hospital	297	33 (58.93)	11.11	7.14	51.79
Yaoundé Military hospital	162	17 (30.36)	10.49	10.71	19.64
Clinique Bastos	87	6 (10.71)	6.9	3.57	7.14
Total	546	56 (100)	10.26	21.43	78.57

3). Women were therefore the most affected by HIV infection according to this study, while men were mostly affected by HCV infection. The mean age was 50.96±11.26 years with 57.3% of people aged over 50 years in PLHIV, compared to a mean age of 36.40±16.77 years in people with HCV. Mean age among HIV/HCV co-infected individuals was higher in the two populations, 58.4±5.32 years and 54.6± 11.55 years respectively for the first and second cohorts, compared to HIV mono-infected people, 50.96±11.26. Also, Mean age in HIV/HCV co-infected men in the two populations (59.00±1 and 63.5±7.78 years respectively) was higher than the mean age in women (58.14±6.47 and 48.66±10.21 years). In total, 93.33% of HIV/HCV co-infected individuals were aged 50 years and above.

Seroprevalence of HIV/HCV co-infection and socio-demographic characteristics

Amongst the 75 HIV-positive patients, ten were also infected by HCV, giving the seroprevalence of 13.3% for HIV/HCV co-infection. Out of 56 HCV positive patients from the cohort of 546 people, five (5) were confirmed HIV positive. The seroprevalence of HCV infection was 10.26% among 546 enrolled participants, and 13.33% in 75 PLHIV (Tables 2 and 4). In the Tables 4 and 5, it is noticeable that the HIV/HCV co-infection seroprevalence is 13.3% in PLHIV but 8.93% among people with HCV infection. HIV/HCV co-infected women were numerous inPLHIV (seven women out of ten patients) as well as in secondary level of education, and civil servants were numerous among HIV/HCV co-infected individual (Table 4). In the population of HCV infected individuals, married people, people with secondary level of education and unemployed were more numerous among the co-infected (Table 5). the other cohort (three out of five), for a total of ten women out of 15 HIV/HCV co-infected individuals, 66.67%. In PLHIV, married people, widowed, people with secondary level of education, and civil servants were numerous among HIV/HCV co-infected individual (Table 4). In the population of HCV infected individuals, married people, people with secondary level of education and unemployed were more numerous among the co-infected (Table 5).

CD4 count analysis

The mean CD4 T-cells in HIV mono-infected and HIV/HCV co-infected patients were 413.68±192.49 cells/ mm^3 and 369.90±235.03 cells/mm^3 respectively. However, the difference was not statically significant. In HIV mono-infected, minimum value obtained was 15 cells/mm^3 and the maximum value was 929 cells/mm^3 whereas in HIV/HCV co-infected, the results show 47 cells/mm^3 and 728 cells/mm^3 respectively for minimum and maximum values (Table 6).

Correlation between different parameters and disease stage

Biochemical parameters (activity of alanine amino-transferase (ALT), aspartate amino-transferase (AST), alkaline phosphatase (ALP), gamma glutamyl-transferase (ɣ-GT), and serum concentration of conjugated bilirubin

Table 3. Distribution of the 56 individuals tested HCV positive within age groups and sex (June to October 2016).

Age group (year)	Female (%)	Male (%)	Total (%)
19 – 30	6 (10.71)	25 (44.64)	31 (55.37)
31 – 40	1 (1.79)	7 (12.50)	8 (14.29)
41 – 50	0 (0)	2 (3.57)	2 (3.57)
>50	5 (8.93)	10 (17.86)	15 (26.79)
Mean age	40.25±19.76 (21-69)	35.65±15.82 (19-77)	36.40±16.77 (19-77)
Total	12 (21.43%)	44 (78.57%)	56 (100%)

Table 4. Socio-demographic characteristics among HIV mono-infected and HIV/HCV co-infected patients in Yaoundé Central Hospital (November 2015 to February 2016).

Sex	Group		
	HIV mono-infected (%)	HIV/HCV co-infected (%)	Total HIV infected (%)
Male	18 (24.0)	3 (4.0)	21 (28)
Female	47 (62.7)	7 (9.3)	54 (72)
Total	65 (86.7)	10 (13.3)	75 (100)
Marital status			
Unmarried	19(25.3)	2 (2.7)	21 (28.0)
Divorced	5 (6.7)	2 (2.7)	7 (9.4)
Married	19 (25.3)	3 (4.0)	22 (29.3)
Widowed	22 (29.3)	3 (4.0)	25 (33.3)
Total	65 (86.7)	10 (13.3)	75 (100)
Education			
Unschooled		0 (0)	4 (5.3)
Primary	26 (34.7)	4 (5.3)	30 (40.0)
Secondary	28 (37.3)	6 (8.0)	34 (45.3)
Higher	7 (9.3)	0 (0)	7 (9.3)
Total	65 (86.7)	10 (13.3)	75 (100)
Occupation			
Civil servants	9 (12.0)	4 (5.3)	13 (17.3)
Other workers	37 (49.3)	3 (4.0)	40 (53.3)
Unemployed	19 (25.3)	3 (4.0)	22 (29.3)
Total	65 (86.7)	10 (13.3)	75 (100)

(CB) were analysed by means of the correlation coefficient “r”. Bivariate correlations between these parameters were searched, in HIV mono-infected as well as in HIV/HCV co-infected patients. Pearson correlation analysis showed a negative and significant correlation between CD4 T cells count and ALT activity (r = -0.241 P = 0.049), and between CD4 cells count and conjugated bilirubin (r = -0.278 P = 0.023) at the threshold 0.05 in HIV mono-infected (Table 7). In HIV/HCV co-infected patients, a positive and significant correlation was observed between ALT and AST activities (r = 0.745 P = 0.013), γ-GT and ALT activities (r = 0.652 P = 0.041), and between total and conjugated bilirubin (r = 0.988, P□0,001) (Table 8).

DISCUSSION

The sampling results showed that among PLHIV recruited, women were the most affected whereas men were the most HCV infected. Actually, women are biologically more vulnerable than men since the mucous

Table 5. Socio-demographic characteristics among HCV mono-infected and HIV/HCV co-infected patients in the three health facilities (June to October 2016).

Characteristics	HCV Mono-infected (%)	HIV/HCV Co-infected (%)	Total (%)
Sex			
Male	42 (80.35)	2 (3.57 %)	44 (78.57 %)
Female	9 (16.07)	3 (5.35 %)	12 (21.42 %)
Total	51 (91.07)	5 (8.93 %)	56 (100 %)
Marital status			
Single	34 (60.71)	1 (1.78)	35 (62.5)
Married	15 (26.78)	3 (5.35)	18 (32.14)
Widowed	2 (3.57)	1 (1.78)	3 (5.35)
Total	51 (91.07)	5 (8.93)	56 (100)
Level of education			
Unschooled	2 (3.57)	2 (3.57)	2 (3.57)
Primary	6 (10.71)	1 (1.78)	7 (12.5)
Secondary	25 (44.64)	4 (7.14)	29 (51.78)
Higher	18 (32.14)	0 (0)	18 (32.14)
Total	51 (91.07)	5 (8.93)	56 (100)
Occupation			
Civil servants	15 (26.78)	1 (1.78)	16 (28.57)
Other workers	8 (14.28)	2 (3.57)	10 (17.85)
Unemployed	28 (50)	2 (3.57)	30 (53.57)
Total	51 (91.07)	5 (8.93)	56 (100)

Table 6. CD4 T cells count and association with HIV mono-infection and HIV/HCV co-infection.

Type of infections	HIV mono-infection	HIV/HCV Co-infection	p-value
Mean CD4 T cells (cells/mm^3)	413.68±192.49	369.90±235.03	0.515
Minimum CD4 T cells (cells/mm^3)	15	47	-
Maximum CD4 T cells (cells/mm^3)	929	728	-

Table 7. Correlation between CD4 count and biochemical parameters among HIV mono-infected patients (N=65).

Variable		Enzyme activity			Serum concentration
		AST	ALT	ɣ-GT	CB
CD4	R	-0.229	-0.241**	0.163	-0.278**
Count	p-value	0.063	0.049	0.187	0.023

surface exposed to HIV during the non-protected sexual relation is larger (Nebout, 1994). Also, the virus attains the high concentrations in the sperm compared to the vaginal secretion, and the HIV transmission frequency in the heterosexual intercourse is most likely to be higher from men to women. In addition, Cameroonian women are more likely to undergo relationship with men older than them, some of whom might have encountered multiple other women partners in their sexual activity history. In short, a multitude of factors increase women's vulnerability to HIV acquirement, including biological, behavioral, socio-economic, cultural and structural risks (Mabala, 2006; Ramjee and Daniels, 2013). Concerning the HCV infection, it is well known worldwide that HCV is

Table 8. Correlation between biochemical parameters in HIV/HCV co-infected patients.

Variable		AST	ALT
ALT	p-value	**0.745****	-
		0.013	-
γ-TG	R	-	0.652**
	p-value	-	0.041

a blood-born pathogen with low sexual transmission rate compared to HIV and hepatitis B virus infections. In Cameroon, a possibility of iatrogenic transmission during the early 20th century has even been hypothesized in a previous study (Pepin et al., 2010), and another study mentioned the HCV infection as a cohort effect (Nerrienet et al., 2005).

With the current study, up to 78.57% men were identified HCV positive, though HIV/HCV co-infected women were still higher in the population of co-infected individuals. This might be due to the fact that in Cameroon, men are less likely to solicited regular medical check-up compared to women. Furthermore, sentinel surveillance in force in Cameroon more than two decades ago has revolutionized the mother and child health care through the prevention of mother-to-child transmission (PMCT) programme. The policy of this programme implies that each and every pregnant woman attending any health facility in Cameroon is systematically screened for HIV, syphilis and hopefully in the near future, hepatitis B and C infections (written strategic plan not yet available).

The project for hepatitis management plan has been initiated in Cameroon in 2015, following the world health organisations (WHO) Global policy report on the prevention and control of viral hepatitis, 2013. It appears in WHO Global policy report that to the question « Is there a written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis? », the response concerning Cameroon was « No » (WHO, 2013). Four years into the remarks, the (written) policies are still in progress.

The seroprevalence of HIV/HCV co-infection was documented in this study: 13.3% in PLHIV and 8.92% in HCV patients, whereas 10.25% were detected HCV positive among 546 individuals. These seroprevalence rates are significantly higher and therefore in discordance with results obtained by previous researchers in hospital settings in Cameroon, as far as HCV infection is concerned (Noubiap et al., 2013; Noubiap et al., 2015; Luma et al., 2016b). This might be in part due to the robustness of the screening test. Previous studies mostly used rapid diagnostic test based on immune-chromatographic principle, or immunoassay detecting antibodies against HCV.

In the presence study, the ultra immunoenzymatic assay for the detection of HCV core antigen and anti-HCV antibodies was used. It has been shown that simoultanous detection of HCV capside antigen and the various antibodies enhances the early detection of HCV infection (Laperche et al., 2005; Tagny et al., 2014). In these studies, the sensitivity and reliability of the assay were well described. Refering to findings in the present study and to the national sero-prevalence for HCV infection in Cameroon in the general poulation, one might affirm that people with HIV are more at risk for HCV infection.

It is well noticeable in the present study that HIV/HCV co-infected as well as HCV mono-infected patients are older, up to 93.3% people aged 50 years and above. Therefore, age appears to be a risk factor. This corroborates findings from other settings: in a study conducted in Central Brazil, increasing age was a risk factor for both HCV and HIV-1 infection among pregnant women (Costa et al., 2009). These results also confirm previous studies on hepatitis viruses' trends conducted in Cameroon, in a secondary used of historical blood samples collected in 2009 during the Demographic and Health Survey and Multiple Indicators Cluster Survey (DHS-MICS), to determine the seroprevalence of hepatitis B, C and Delta infections. Data analysis indicates that in Cameroon, HCV infection in the general population account for about 1.03%, but is higher in the elder populations: HCV seroprevalence varies from 1% in people under 45 years of age, to 3% between 45-55 years and 7% in people above 55 years respectively (Njouom and Tejiokem, 2016).

Analysing the CD4 T cells count, it was subject to variation in co-infected individuals without any significant difference in mean CD4 count between HIV mono-infected and HIV/HCV co-infected participants (p=0.515): patients with HIV/HCV co-infection had a low mean CD4 T-cells count together with a high standard deviation, 369.90±235.03 cells/mm3compared to mean CD4 T-cells count and standard deviation in HIV mono-infected participants, 413.68±192.49. In addition, the analysis of the minimum and the maximum CD4 T-cells count values in the two groups shows that the lowest CD4 count value was observed in the HIV mono-infected groups, but a low maximum value observed in HIV/HCV co-infected patients. This magnitude of CD4 T-cells count in HIV/HCV co-infected could be due to the pressure by the two viruses on the human organism. This might be attributed to reduced immunity (immune suppression) in HIV positive patients leading to vulnerability to other opportunistic infections. This study ends-up by the following observation: two (2) in every 15 people with HIV are HIV/HCV co-infected.

The negative and significant correlation observed between CD4 T-cells count and ALT, CD4 count and conjugated bilirubin in HIV mono-infected patients proves

that CD4 T-cells decrease, enabling progression of AIDS, while ALT and conjugated bilirubin increase, sign of liver deterioration. In HIV/HCV co-infected patients, ALT activity increases with AST and γ-GT activities, and this is an indicator of liver deteriorating liver function in these populations.

Conclusions

Hepatitis C virus infection is a threat in people living with HIV in Cameroon: the seroprevalence of HCV infection is significantly higher amongst HIV positive patients than in the general population in Cameroon. Women are more at risk with a high HIV seroprevalence rate. Age tends to be a risk factor. Also, correlation investigation indicates that when biochemical parameters of the liver function are elevated, the immuno-depression is observed. It is important and urgent that disease awareness is implemented in health facilities, that written national strategic plans that focuses exclusively on the prevention and control of viral hepatitis and co-infections are not only set up, but be functional. Follow-up of people living with HIV shall include the identification of acute and chronic HCV carriers; future investigation of HCV persistence and infectivity of representative isolates from around the world might be useful worldwide in improving widely accessible drugs and vaccine development.

RECOMMENDATIONS

Based on the present research findings, a national management and active surveillance program for HIV and hepatitis co-infections is essential in the country, as a critical step to reduce the incidence and morbidity rates of these affections. The new policies shall integrate and consider viral hepatitis as serious as HIV infection. In addition, the screening algorithms should integrate rapid diagnostic tests as well as enzyme-immunoassays.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The present study satisfied the national and international ethical standards: Ethical clearance was obtained from the Cameroon National Research Ethics Committee for Human Health, prior to the study implementation (Authorizations N°2015/11/664/CNERSH/SP and N°2016/06/779/CNERSH/SP). In addition, informed consent was obtained from each enrolled participant. The study was conducted according to the CIOMS guidelines, and complied with the Declaration of Helsinki, 2015. Participants gave their authorization that samples are transferred for future investigations from Cameroon to United States under safety conditions, together with CDC permit and a duly executed MTA between the providing and the recipient institutions.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Time for initiation of antiretroviral therapy in HIV co-infected tuberculosis patients in Addis Ababa, Ethiopia

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Provision of integrated care for human immunodeficiency virus (HIV) co-infected tuberculosis (TB) patients is challenging. Many persons with TB and HIV co-infection are not yet receiving anti-retroviral therapy (ART) and initiation of ART is not always timely. This study investigated ART uptake among HIV co-infected TB patients and its time of initiation in an urban primary health care facility in Ethiopia. A retrospective cohort study was conducted using routine program data. All adult HIV co-infected TB patients registered in a large TB-HIV clinic in Addis Ababa from September, 2008 to August, 2014 were included. Both descriptive and inferential statistics were used to summarize and analyse findings. A total of 993 TB patients were registered in the study period and included. HIV counselling and testing was offered to 738 (74.5%) and HIV testing was performed for 678 (68.3%) patients. Of those tested, 226 (33.3%) were HIV co-infected of whom 125 (57.6%) were started on ART. The median period from commencement of TB treatment to starting of ART was 41 days. ART initiation was delayed beyond the period advised in the National TB-HIV Guideline for 31 (27%) of HIV co-infected TB patients. For 109 (48.2%) of co-infected TB patients the ART status evaluation could not be done due to missing data. A considerable proportion of HIV co-infected TB patients did either not receive ART or started it later than recommended by national guidelines. For better outcomes to HIV co-infected TB patients, the actual implementation of national recommendations on when to start ART needs to be monitored closely.

Key words: ART-uptake delay, TB-HIV, primary health facility.

INTRODUCTION

Screening of all tuberculosis (TB) patients for human immunodeficiency virus (HIV) co-infection and referral of HIV positive patients for antiretroviral treatment (ART) initiation and chronic care services are essential

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components of collaborative TB-HIV activities and crucial to reduce mortality and morbidity in TB patients (FMOH, 2007; Sileshi et al. 2013). Medical management of HIV co-infected TB requires standardized anti-TB treatment combined with trimethoprim-sulphamethoxazole (co-trimoxazole) prophylactic therapy (CPT) and ART (WHO, 2010).

The recommended timing of ART initiation after TB treatment start has been adapted several times in the last decade based on the available evidence (Lawn et al., 2009). The latest insights are that early initiation of ART started within 2 weeks of commencing TB treatment, in all HIV co-infected TB patients regardless of CD4 count significantly improves survival (Abdool Karim et al., 2010; Nglazi et al., 2015) and is particularly beneficial for patients with CD4 counts <50 cells/µl (Franke et al., 2011; Salim et al., 2011; Naidoo et al., 2013; Stockdale et al., 2013).

In 2014, globally, 51% of notified TB patients had a documented HIV test result and 77% of TB patients known to be HIV co-infected started ART. In Ethiopia with a high burden of both TB and HIV, 75% of TB patients had a documented HIV test result while only 39% of HIV co-infected TB patients had started ART (WHO, 2014) .

The National Ethiopian TB-HIV guideline was revised in 2007 and 2013 specifically with regards to timing of ART and how to prioritize HIV co-infected TB patients for ART initiation (FMOH, 2007; 2013). The 2007 guideline recommended ART to be started within 8 weeks of commencing TB treatment for patients with a CD4 count <200/µl and at completion of the intensive phase of TB treatment for patients with a CD4 count of 200 to 350/µl while deferring ART commencement for those with a CD4 count >350/µl. The updated Ethiopian TB-HIV 2013 guideline following new global guidance recommends ART initiation as soon as TB treatment is tolerated (usually within 2 to 8 weeks) for those with a CD4 count <200/µl, to start within 8 weeks of starting TB treatment for TB co-infected patients with a CD4 count ranging from 200 to 350/µl, while it is recommended to defer ART and reassess at 24 weeks or at completion of TB treatment for those with a CD4 count >350/µl. Whether or not the National guideline is fully adhered to and TB co-infected patients are started timely on ART, is not known.

The objective of this study was to investigate ART uptake among HIV co-infected TB patients and timing of ART initiation in an urban primary health care facility, against the standard of care as described by the Federal Ministry of Health of Ethiopia in the National TB/HIV guidelines.

METHODOLOGY

Study design and setting

A retrospective analysis of routine program data was carried out in a primary health facility in Addis Ababa. Addis Ababa, the capital city of Ethiopia, has an estimated population of 3 million (FDRE Population Census Commission, 2007). Addis Ababa regional health bureau oversees 11 hospitals and 26 health centers which provide comprehensive health services for its urban residents. Diagnostic and treatment services for TB and HIV are provided at both the hospital and health center level. Patients who cannot be managed at the health center level are referred to the hospital. Bole 17 health center is located in Bole sub-city of Addis Ababa. This health center is one of the first primary health care facilities to start HIV care in the city, including ART initiation and follow up. An average of 40 people living with HIV and TB attend this clinic every year

In Ethiopia, HIV co-infected TB patients are referred to ART clinics to be registered and assessed for ART initiation according to the prevailing National TB/HIV guideline. For the study, delay in starting ART was defined as: eligible HIV-co infected TB patients starting ART beyond the period indicated in the prevailing national guideline for TB/HIV collaborative activities at the time of TB treatment start, which is either the 2007 or 2013 edition of the guidelines. As per the guideline, eligibility is identified based on CD4 count, presence of opportunistic infections and WHO clinical stage. Most of the TB patients are diagnosed and start treatment at the health centre although the health centre also receives TB patients diagnosed elsewhere to start or continue TB treatment. All TB patients are offered HIV testing and counselling and HIV co-infected TB patients are referred to the ART clinic in the same health centre to be enrolled into HIV care. One health officer and one nurse are full time employed in the TB clinic with other trained health professionals providing help based on needs.

Sampling technique and study variables

For this study, all adult TB patients (>18 years) registered at Bole 17 Health Center from 1 September, 2008 to 31 August 2014 were included in the study. Patients who were already on ART before TB diagnosis were excluded. Sources of data were unit TB registers and ART registers. Patients registered for TB treatment from September, 2008 to March, 2013 were assessed against the 2007 guideline and those registered for treatment from April, 2013 to August, 2014 against the revised 2013 guideline (FMOH, 2007, 2013). The main outcome, delay in ART initiation was determined by calculating the difference between start date of TB treatment and start date of ART treatment, which is then compared with national TB/HIV management guideline on when to start ART for co-infected patients**.** Explanatory variables collected were age, sex, site of TB infection, pulmonary TB smear result, TB treatment history, TB treatment start date, HIV test offered, HIV testing done, HIV test result, HIV test date, CPT provision, CPT start date, enrolment to HIV care, date of enrolment to HIV care, WHO clinical stage at enrolment, CD4 cell count, recipient of ART, ART start date, opportunistic infection (OI) diagnosis, outcome of TB treatment, and timing of ART (that is, time between TB treatment start and ART start).

Data management and analysis

The data were double entered and analyzed using SPSS Version 2.0 statistical package (SPSS Inc'). Description of means, frequencies and proportions were used to describe all study variables. Bivariate analysis was performed to test for associations between each explanatory variable and the outcomes of interest. Explanatory variables that were found to be significant in bivariate analysis were included in a multivariate logistic regression model. This estimated the relative effect of the explanatory variables in predicting the outcomes of interest. A P-value ≤ 0.05 was considered as a statistically significant association and the adjusted odds ratio with 95% CI was calculated.

Table 1. Characteristics of tuberculosis patients registered in Bole 17 health center, Addis Ababa, Ethiopia, in 2008-2014.

Patient characteristics	Frequency (n)	Percentage
Sex, n=993		
Male	510	51.4
Female	483	48.6
Age, n=993		
18-24	298	30.0
25-39	447	45.0
≥40	248	25.0
Type of TB* disease by site, n=993		
Pulmonary	606	61.0
Extra-pulmonary	387	39.0
Pulmonary TB, n=606		
Smear positive	340	56.0
Smear negative	266	44.0
Type of TB by treatment history, n=993		
New	947	95.4
Retreatment	46	4.6
Year started TB treatment, n=977		
2008-2009	219	22.4
2010	205	21.0
2011	176	18.0
2012	265	27.1
2013/2014	112	11.5

*- tuberculosis

Ethical consideration

Ethical approval was obtained from the Ethical Review Committee of the Addis Ababa Regional Health Bureau and permission was obtained from the Tuberculosis Research Advisory Committee (TRAC) and the Bole 17 health center.

RESULTS

Patient characteristics

A total of 993 TB patients were registered over the six year period. Their median age was 29 years (inter-quartile range (IQR) 23 to 39) and 510 (51%) were male. The majority 947 (95%) patients had a first episode of TB (so called new patients) and 606 (61%) had pulmonary disease. Of the 606 pulmonary TB patients, 340 (56%) were sputum smear- positive for acid-fast bacilli (Table 1). The majority of TB patients 904 (91%) were evaluated against the 2007 guideline and the rest 88 (9%) were evaluated against the revised 2013 guideline.

HIV status and CPT and ART uptake

HIV counselling and testing was offered to 738 (74.5%) of the 993 TB patients and HIV-test was performed for 678 (68.3%) of whom, 226 (24.4%) tested HIV positive (Figure 1). Of the 226 HIV co-infected patients, 189 (83.6%) were enrolled in HIV care and 125 (57.6%) had started ART, while 200 (94%) were started on CPT. For 203 (89.8%) HIV co-infected TB patients, staging information was available with 165 (81.2%) being WHO stage 3 and 38 (18.7%) being WHO stage 4 (Table 2). Data on CD4 count was available for 191 HIV positive patients (86.7%): 17 (8.9%) had a CD4 count of <200/µl, while 113 (59.2%) had CD4 between 200 and 350, with remaining 61 >350/µl.

Table 2. Clinical stage, CD4 count, and opportunistic infection and ART status of TB positive HIV patients in Bole 17 health center from September 2008 to August 2014.

Characteristic	Frequency	Percentage
HIV testing		
Yes	678	68.3
No	9	0.9
Not recorded	306	30.8
WHO clinical stage		
3	165	81.3
4	38	18.7
CD4 cell count per µl		
<200	17	8.9
200-350	114	59.9
>350	60	31.3
Opportunistic infections (OIs) diagnosed, n=160		
Yes	20	12.5
No	140	87.5
CPT started		
Yes	200	94.3
No	4	1.9
Not recorded	8	3.8
ART started		
Yes	125	57.6
No	73	33.8
Not recorded	19	8.8

Timing of ART initiation

Of the 226 HIV co-infected TB patients, only 121 (53.4%) had information on the start dates of both TB and ART treatment. Timing of ART initiation after start of TB treatment was computed for these 121 patients. The median time period from TB treatment start to ART initiation was 41 days (IQR: 25 to 84 days). Timeliness of ART initiation was analyzed against the 2007 and 2013 national guideline as outlined in the methods. Of the 117 patients assessed against the 2007 guideline, for 31 (26.5%), ART initiation was delayed (Figure 1). The four patients assessed against the 2013 guideline all had started ART within the required timeframe.

Determinants of timing of ART initiation

Of the factors (age, sex, type of TB by site, smear result, treatment history, year that TB treatment started, CD4 cell count, WHO clinical stage and presence or absence of opportunistic infections) evaluated for association with timing of ART initiation, only CD4 cell count was found to be statistically significantly associated in multivariate analysis. Patients with CD4 counts less than 50/µl were three times more likely to start ART in a timely manner when compared to patients with CD4 count greater than 200/µl ($p<0.005$) (Table 3).

TB treatment outcomes among HIV co-infected TB patients

Of the 226 HIV co-infected TB patients, 119 (54.1%) completed TB treatment and an additional 38 (17.3%) had documented cure, resulting in a successful TB treatment outcome for 71.4% of HIV co-infected patients. A total of 61 (27.4%) of the patients had undesirable outcomes (died (9.5%), transferred out (9.5%), defaulted (7.0%) and treatment failure (1.4%)). For 3.2%, no treatment outcome was recorded (Table 4). In HIV-negative TB patients, a treatment success rate of 82.7% was observed (Table 4). TB treatment success rate was significantly associated with HIV status (P value < 0.001)

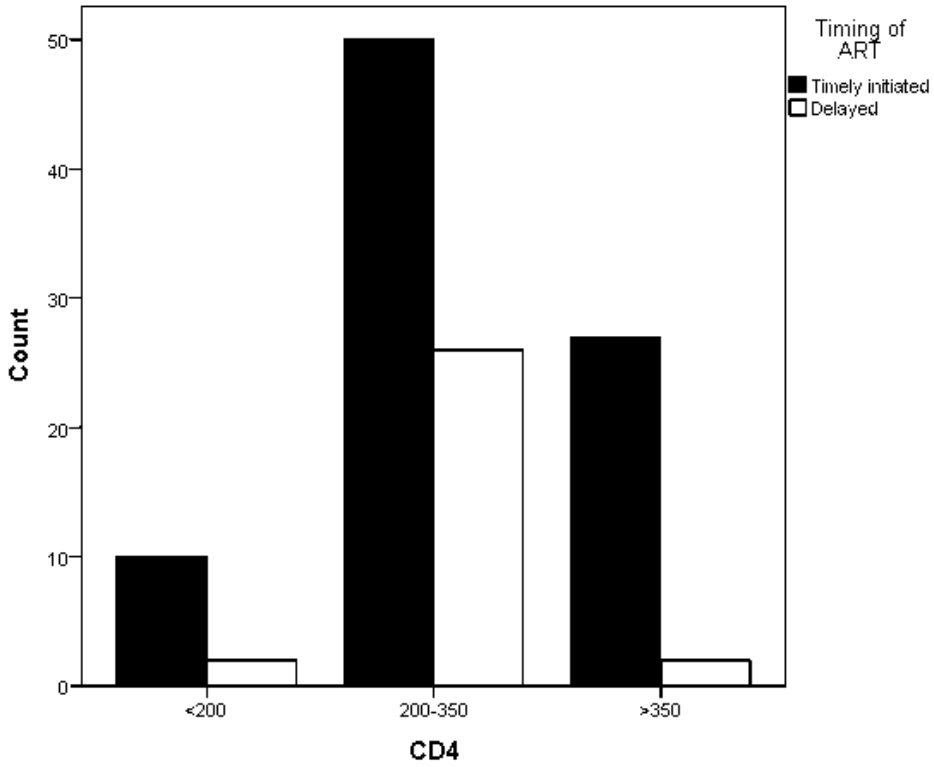

Figure 1. Percentage of patients delayed from ART treatment after they started TB treatment versus CD4 count category in Bole 17 Health centre, Addis Ababa, Ethiopia, September, 2008 to August, 2014.

with HIV negative TB patients being 2 times more likely to have a successful treatment outcome.

Timing of ART initiation and TB treatment outcome

Of the 226 HIV co-infected TB patients, 21 (9.5%) died of whom 7 (36.5%) were started on ART, with one starting ART late. ART initiation showed a significant association with TB treatment success (P value=0.01) with those not started on ART being 2 times more likely to have an undesirable treatment outcome. ART initiation, ART delay and CD4 count showed no significant association with patient mortality (Table 5). Looking at TB treatment outcome in relation to timing of ART initiation indicated no statistical difference in treatment outcome for those starting ART as per guideline compared to those who started ART late in this study.

DISCUSSION

WHO recommends time of initiation of ART uptake in HIV co-infected TB patients in relation to starting of TB treatment as a core indicator for programmatic evaluation of collaborative TB/HIV activities, as indicated by TB/HIV indicators for monitoring and evaluation B8 and B9 (World Health Organization, PEPFAR, UNAIDS, 2015). In the current study the time between TB treatment initiation and ART initiating was a median of 41 days (IQR: 25 to 84 days). Less than two thirds of HIV co-infected TB patients (57.6%) were started on ART of whom 27% started ART later than recommended per the National Ethiopian, as well as the global guidelines. This is a cause for great concern as the latest global guidelines of WHO and UNAIDS of 2015 advise that all HIV co-infected TB patients should be started on ART within 2 months after start of TB treatment, and those with a CD4 counts of less than 50 be started as soon as possible within 2 weeks (World Health Organization, 2015). Other countries in the region have reported much better results in ART initiation. An observational cohort study carried out among HIV positive TB patients in South Africa (Lawn et al., 2011) reported that 87% started on ART while in a study in Kenya this was 70% (Tayler-Smith et al., 2011). Both countries have adopted the recent WHO guideline that all TB patients (irrespective of CD4 count) are started on ART within two months of start of TB treatment. The lower observed proportion of TB patients starting ART in Ethiopia could be due to differences in the national guidelines as the National guideline in Ethiopia does not yet recommend start of ART irrespective of CD4 in line

Table 3. Factors associated with Timely vs. late ART initiation by CD4 cell count with respect to initiation of TB treatment of TB positive HIV patients in Bole 17 health center from 2008 to 2014.

Patient characteristic	Factors associated with earlier vs. late ART initiation with respect to initiation of TB treatment	
	Crude OR, 95% CI	Adjusted OR (95% CI, P-value)
Age		
18-24	0.424 (0.076, 2.373)	0.130 (0.003, 5.156)
25-39	0.986 (0.367, 2.651)	2.430 (0.535, 11.037)
≥40	1	1
Sex		
Male	1	
Female	0.436 (0.183,1.038)	
Type of TB disease by site		
Pulmonary	1.816 (0.727, 4.534)	
Extra pulmonary	1	
Pulmonary TB		
Smear positive	1.148 (0.411, 3.212)	0.882 (0.240,3.232)
Smear negative	1	1
Type of TB by treatment history		
New	0 .999 (0.00)	
Retreatment	1	
CD4 cell count (per µl)		
<50	3.213 (1.896, 5.446)	3.784 (2.073, 6.909)
50-200	1.573 (.0.888, 2.785)	1.09 (0.531, 2.238)
>200	1	1
WHO stage		
3	2.400 (0.936, 6.151)	0.992 (0.126, 7.838)
4	1	1
Opportunistic infections (OIs) diagnosed		
Yes	1.050 (0.259, 4.249)	1.128 (0.193, 6.607)
No	1	1

with the latest global recommendations. The guidelines are currently being updated to be in line with the latest global guidance.

Also, poor recording and reporting could have affected the findings, as for nearly 50% the timeliness of ART could not be determined as both the dates of ART initiation and TB treatment start were not available. This calls for better routine recording and reporting to ensure that program data can be used to asses program performance. At the same time as being a limitation, use of routine data was the main strength of the study as despite the shortcomings, the findings likely reflect the operational reality on ground.

In the current study, CD4 count was found to be a predictor for timing of ART where patients with lower CD4 count were more likely to be put on ART in a timely manner. This was also the case in other studies where ART is not considered when the CD4 count is high (Chilton et al., 2008).

CPT was well implemented, with nearly 95% of eligible patients started on CPT. This was higher than CPT uptake reported in another study carried out in Addis Ababa which reported that only 43.6% patients benefited from CPT (Denegetu and Dolamo, 2014) while in a referral hospital in North-West Ethiopia, 45.9% of patients eligible for CPT actually received treatment (Alemayehu

Table 4. Tuberculosis treatment outcomes of HIV co-infected and HIV-negative TB patients in Bole 17 health center 2008 to 2014.

Characteristic	Frequency (n)	Percentage
HIV positive		
Cured	38	17.3
Treatment completed	119	54.1
Died	21	9.5
Failure	3	1.4
Defaulted	16	7.0
Transferred out	21	9.5
Not recorded	7	3.2
HIV negative		
Cured	201	28.8
Treatment completed	377	53.9
Died	18	2.6
Failure	9	1.3
Defaulted	27	3.9
Transferred out	45	6.4
Not recorded	22	3.2

Table 5. Factors associated with mortality among HIV co-infected TB patients in Bole 17 health center from 2008 to 2014.

Patient characteristic	Factors associated with patient mortality	
	Crude OR, 95%CI	Adjusted OR,95%CI
CPT started		
Yes	0.603 (0.144, 2.532)	-
No	1.000	-
HIV care enrolled		
Yes	0.360 (0.046, 2.808)	-
No	1.000	-
WHO stage		
Stage 3	0.828 (0.266, 2.584)	0.429(0.068,2.724)
Stage 4	1.000	1.00
ART started		
Yes	0.390 (0.147, 1.035)	-
No	1.000	-
OI diagnosed		
Yes	2.035 (0.531, 7.797)	2.318(0.244,22.040)
No	1.000	1.00
Delay ART		
No	2.120 (0.245,18.380)	1.249(0.124,12.557)
Yes	1.000	1.00

et al., 2009). Besides, a 10-year review of the scale-up of TB and HIV program collaborative activities in Zambia revealed CPT coverage of 70% in 2010 (Kapata et al., 2012). The possible reasons for a relatively higher CPT

uptake in the present study might be attributed to trainings provided to health workers on importance of initiation of CPT.

Conclusions

The median time to start ART after commencement of TB treatment was 41 days and 27% of HIV co-infected TB patients started ART late if evaluated against the prevailing national guideline. Early ART initiation in TB patients is a life saving intervention and through consistent follow-up and training of health workers it should be ensured that all HIV positive TB patients receive ART as per the latest national guidelines. Recording and reporting of patient information should be improved through regular follow-up and mentoring of health care providers to ensure that quality data can be used to guide programs. TB/HIV collaborative activities should be strengthened to ensure timely ART initiation.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Full Length Research Paper

Pattern and predictors of cluster of differentiation 4 (CD_4) cell count recovery among cohorts of human immunodeficiency virus (HIV)-infected patients on antiretroviral therapy in Hawassa University Referral Hospital

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Cluster of differentiation 4 (CD_4) cell count recovery is used in determining disease progression and outcome monitoring. This study was conducted to determine the trends of CD_4 cell count recovery, and its determinants in Hawassa university referral hospital, Ethiopia. Retrospective cohort study design was employed to gather relevant data among human immunodeficiency virus (HIV) positive-patients visiting Hawassa University referral hospital. Data were collected from December 1, 2014 to May 15, 2015. A total of 2400 medical records of adult patients aged above 15 years were examined. Of these, 1479 were evaluated and analyzed. Multivariate logistic regression was constructed to determine predictors of change in CD cell count. The median change in CD_4 cell count from baseline to six months was 124 cells/µl. 19.3% of patients were at risk of immunologic non-response at 12 months of treatment. Patients with a baseline CD_4 cell count of less than 100 cells/ml were 5 times more likely to exhibit immunologic non-response compared to those with a baseline CD_4 cell count > 350 cells/µl. Baseline body mass index (BMI) and sex were associated with failure to attain ≥200 cells/µl at 12 months of treatment. Rapid recovery of CD_4 cell count occurred during the first six months of treatment in this study. However, significant proportions of patients were at risk of immunologic non-response. Low baseline CD_4 cell counts were predictive of non-response in this setting. The findings suggest that initiation of antiretroviral therapy (ART) at a CD_4 cell count greater than 500 cells/µl is associated with better immune recovery.

Key words: Antiretroviral therapy, CD4 cell count, HIV/AIDS, Ethiopia.

INTRODUCTION

Antiretroviral therapy (ART) began in Ethiopia in 2003, and was made freely available in 2005. An estimated 769,500 Ethiopians are currently living with human immunodeficiency virus (HIV), of whom 542600 require ART and 367 000 are currently taking the treatment (FDRE, 2014).

Recognizing the need for ART, the government of Ethiopia issued the first ART guidelines in 2003. Revisions were issued in 2005, 2008 and 2014 to facilitate a rapid scale-up of the service (FDRE, 2014; FMOE, 2008; MoH, 2005). These guidelines recommended measurement of CD4 cell count every six months as a major tool for monitoring treatment outcome.

In a resource limited setting like Ethiopia, where viral load determination is expensive, CD_4 cell count will remain an important tool for monitoring response (FDRE, 2014). ART is celebrated for its reduction of mortality. The mortality rate was 15.4 per 100 person-years of observation (PYO) in the highly active antiretroviral therapy (HAART) group, and in the pre-HAART group it was 58.1 per 100 PYO in an early study conducted in Ethiopia (Jerene et al., 2006b). However, mortality is higher in Ethiopian cohorts than in patients in developed world (Jerene et al., 2006b; Jerene et al., 2006a; Johansson et al., 2008). Higher mortality is partly attributed to delay in the initiation of treatment, at a time when the disease has progressed to a state of severe immune depletion (Jerene et al., 2006b; Berhe et al., 2012).

Studies examining the association between baseline CD_4 cell count and immune recovery following ART report conflicting results. It has been reported that higher baseline CD_4 count is associated with reduced early mortality (Stephen et al., 2008), and counts of less than 50cells/µl is associated with high mortality in both experienced and naive patients on HARRT (Zachariah et al., 2006; Evan et al., 2003).

Some studies have revealed that a significant percentage of HIV-infected patients who initiate therapy with a low baseline CD_4 cell count do not achieve a normal CD_4 cell count, even after a decade of effective treatment (Lange et al., 2002; García et al., 2004; Lederman et al., 2003; Kaufmann et al., 2002). Other studies indicate patients with low baseline CD_4 cell count achieve better CD_4 cell recovery compared to those with high baseline CD_4 level (Lawn et al., 2006). In another study, researchers report no association between baseline CD_4 cell count or viral load, and immunologic or virologic response after commencement of ART (Kilaru et al., 2006).

The survival rates of human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) patients in Ethiopia can be improved given the factors responsible for death in Ethiopian cohort of patients initiating ART are well explored. One possible explanation for high mortality in Ethiopia is that treatment in Ethiopia begins after sever immunosuppression. There are, however, conflicting results in the literature about advantage of early initiation before sever immune damage. Given that, factors affecting CD_4 cell count recovery after ART is unclear in Ethiopia setting, this paper explores such factors. Furthermore, there are few large-scale studies examining immunological correlates, with long-term follow-up, of Ethiopian patients.

We present the overview of the trends of CD_4 cell count recovery and its determinants in an Ethiopian patient population using routinely available clinical data.

METHODOLOGY

Study area

The study was conducted in Hawassa University Referral Hospital, a major referral hospital serving over 15 million people in a region located 270 kilometers south west of Addis Ababa, Ethiopia. The hospital provides general service including HIV/AIDS comprehensive care and treatment.

Study design

We used a retrospective cohort study design to gather relevant data from the records of HIV positive-patients who visited the hospital between 2005 and 2014.

Study period

Data was collected from December 1, 2014 to May 15, 2015.

Inclusion and exclusion criteria

Patients older than fifteen years old during the initiation of the treatment and initiated treatment at Hawassa University hospital, and whose patient record included the information necessary for the current study were included. Patients with competing causes of death (cause of death other than HIV, those with immune compromising chronic diseases such as diabetes, thyroid disease, or any non-AIDS malignancies) were excluded.

Sample size

A total of 2400 medical records met the age requirement from a total 2,950 medical records. About 550 medical records of pediatric (ages less than 15) were excluded. Data collected from 921 medical records were excluded because they have missing baseline and six month CD_4 cell count. Therefore, 1479 medical records included sufficient information for inclusion in the current study, were evaluated and analyzed. Secondary data were extracted from the ART register database, and unique identities were assigned to these records.

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Data collection tool

We used a data collection tool that was previously described, and that was developed using the federal ministry of health HIV care/ART entry and follow-up forms used in the ART clinic of the Hospital (Naftalin et al., 2015; Mutimura et al., 2015; Luz et al., 2014; Kanters et al., 2014; Calmy et al., 2012; Boulassel et al., 2012; Wright et al., 2011; Waters et al., 2011; Okulicz et al., 2010; McKinnon et al., 2010; Lok et al., 2010). Data sources included the pre-ART registration, lab requests, monthly cohort and follow up forms, the ART intake form, the patients' card, and the death certificate. We additionally examined the home visitors' registration, and records of phone calls made by drug adherence professionals, or that revealed death of a patient following inquiries about missed appointment. Where baseline CD4 levels were not measured we relied on tests performed within one month before ART was initiated.

Study variables

The data extraction form includes the following variables: socio-demographic characteristics (age, sex, height, religion, marital status, educational status), baseline laboratory values (CD4 cell count)**,** world health organization (WHO) clinical staging**,** duration on ART**,** and **r**egimen type)

Data quality assurance

Data was collected by counselor nurses trained in comprehensive ART, working in an ART clinic. Data quality was assured with the help of the data collection tool through routine cross-checking of data on a daily basis. Data collection forms were examined for completeness and consistency during data management, storage, and analysis by investigators. A pilot study was conducted in order to test consistency of the tool, and to ensure data quality. The tool was revised using feedback from the pilot study. Data encoded and edited by the principal investigator was checked by co-investigators.

Operational definitions

Change in CD_4 cell count

A general term used to quantify immunologic recovery. In this paper it is measured as: baseline-to-six-month median change in CD4 cell count, the median six-month-to-12-month change, immunologic non-response, and failure to attain 200 cells/µl

Baseline-to-six-month median change in CD4 cell count

The difference between the median of six months measurement and baseline measurement was recoreded.

The median six-month-to-12-month change

The difference between the median of 12th month measurement and 6th month measurement was recorded

Immunologic non-response

An increase of <50 cells/µl, following 12 months of treatment and was calculated using data from records that included a CD^4 cell count at baseline, and at 12 months of treatment (n=1140).

Failure to attain ≥200 cells/µl following 12 months of treatment

This response measure used to quantify non-response in subsample of those who had baseline CD_4 cell count of < 200 cells/µl was calculated using data from records that included a CD4 cell count at baseline, and at 12 months of treatment (n=681)

Baseline CD_4 cell count

The CD4 cell count was measured just during the initiation of treatment in treatment of naïve-patients.

Ethical statement

Ethical clearance was obtained from Hawassa University Medicine and Health Science College Institutional Review Board. Written consent could not be obtained for this retrospective study so the investigators were authorized by the institutional review board (IRB) to use the data after de-identification prior to collection.

Statistical analysis

Data were entered and analyzed using statistical package for social sciences (SPSS) for Windows, version 20. Patient cohort characteristics were described in terms of mean/median value for continuous data and percentage for categorical data. Multivariate logistic regression was constructed to determine predictors of change in CD cell count, factors determining non-response, and failure to attain a CD_4 count of 200 cells/µlfollowing12 months of treatment. All statistical tests were considered significant if the two-sided P-value was<0.05.

RESULTS

Socio-demographic profile of the study participants

Routinely collected data from a total of 1479 medical records of HIV-infected patients on HAART were reviewed and analyzed. At baseline, 90% of the cohort where under the age of 45 years with a mean (SE) age of 33.3(0.23). 62.4% were female, 54.4% were married and 9.5% were pregnant. 37.1% had attained secondary-level education and 14.4% were illiterate. Complete socio-demographic profiles of the study population are listed in Table 1.

Clinical profiles of the patients

More than one-third of the patients (38.7%) initiated treatment with a TDF+3TC+EFV regimen. At baseline, more than half of the study participants (53.7%) were in clinical stage III. 694 (46.9%) patients had a normal BMI at baseline and 258 (17.4%) were underweight. Clinical

Table 1. Socio-demographic characteristics of the HIV positive-patients (n=1479).

Variable	Female	Overall Frequency	Valid frequency
Sex	Female	923 (62.4)	62.3
	Male	556 (37.6)	37.7
Age	‹25	166 (11.2)	11.3
	25-45	1169 (79.0)	79.9
	≥45	128 (8.7)	8.7
	Missing	16 (1.1)	
Education status	Illiterate	210 (14.2)	14.4
	Primary	504 (34.1)	34.7
	Secondary	549 (37.1)	37.8
	Tertiary	191 (12.9)	13.1
	Missing data	25 (1.7)	
Marital status	Never married	212 (14.3)	14.5
	Married	805 (54.4)	54.9
	Separated	140 (9.5)	9.5
	Divorced	115 (7.8)	7.8
	Widowed	194 (13.1)	13.2
	Missing data	13 (0.9)	
Pregnancy status at initiation	Pregnant	140 (9.5)	9.9
	Non-pregnant	722 (48.8)	50.8
	Not applicable (male)	558 (37.7)	39.3
	Missing	59 (4.0)	-

profiles of the full patient population are listed in Table 2.

Pattern of CD_4 change

Of the total 1479 patient records, 1460 (98.71%) included measures of CD4 cell count at baseline. The median and mean CD_4 cell count at baseline was 161 and 172 cells/µl, respectively. At six months of treatment measures reached 285 and 311 cells/µl, respectively. The baseline-to-six-month median change in CD_4 cell count was 124, and the median six-month-to-12-month change was 24 cells/µl. The mean increase in CD4 cell count from baseline to six months was 138, and from six months to 12 months was 20 cells/µl. We observed that most CD_4 cell recovery occurs during the first six months (Figure1). Pattern of six monthly changes in CD_4 cell count at and after the commencement of ART are shown in Figure 1. The overall median CD_4 cell count increased continuously for 6.5 years. The CD_4 cell count declines at 78 months (Figure 2).

About 19.3% of study participants exhibited immunological non-response (Table 3). Association between various variables (sex, age, baseline CD_4 count, WHO stage, BMI and baseline regimen type) and non-response were tested. Baseline CD_4 cell count was significantly associated with immunologic non-response after 12 months of treatment: patients with low CD_4 cell count have greater odds of non-response rate than those with high baseline CD_4 cell count. Those with a baseline CD_4 cell count of less than 100 cells/µl had a greater chance of non-response (crude odds ratio (COR) = 6.27, 95% CI: 2.98- 13.16) compared to those with a CD_4 cell count greater than 351 (Table 3).

Multivariate logistic regression analysis revealed that baseline CD_4 cell count is an independent predictor of subsequent CD_4 cell count recovery. Patients with baseline CD_4 cell <100 cells/µl were five times more likely to exhibit immunologic non-response compared to those with a baseline CD_4 cell count>351 cells/µl (adjusted odds ratio (AOR) = 5.17, 95% CI: 2.17-12.32) (Table 3).

We further examined those that failed to reach a CD_4 cell count of >200 cells/ µl at 12 months of treatment in subsample of those who had baseline CD_4 cell count of < 200 cells/µl. Sex, BMI and baseline regimen type were associated with failure to reach 200 cells/µl at 12 month

Table 2. Baseline clinical characteristic of the HIV positive-patient.

Baseline variable	Female	Overall Frequency	Valid frequency
Regimen type	TDF+3TC+EFV	573 (38.7)	38.7
	TDF+3TC+NVP	103 (7.0)	7.0
	AZT+3TC+EFV	194 (13.1)	13.1
	AZT+3TC+NVP	182 (12.3)	12.3
	D4T+3TC+EFV	195 (13.2)	13.2
	D4T+3TC+NVP	232 (15.7)	15.7
WHO stage	I	172 (11.6)	11.7
	II	317 (21.4)	21.7
	III	788 (53.3)	53.7
	IV	191 (12.9)	12.9
	Missing	11 (0.7)	-
Patient status during initiation	Ambulatory	365 (24.7)	25.2
	Bedridden	90 (6.1)	6.2
	Working	994 (67.2)	68.6
	Missing	30 (2.0)	-
BMI category	Underweight (≤ 17)	258 (17.4)	24.3
	Normal (18-25)	694 (46.9)	65.3
	Overweight (26-30)	94 (6.4)	8.9
	Obese ≥ 31	16 (1.1)	1.5
	Missing	417 (28.2)	-
Baseline CD4 category (cells/µl)	<100	426 (28.8)	29.2
	101-250	726 (49.1)	49.7
	251-350	225 (15.2)	15.4
	>351	83 (5.6)	5.7
	Missing data	19 (1.3)	-
CD4 cell count change at 12 months (%)	<50	220 (14.9)	19.3
	≥50	920 (62.2)	80.7
	Missing	339 (22.9)	-
CD4 cell count at 12 months (for baseline CD count less than 200 cells/µl)	Still <200	53	7.8
	>200	628	92.2

of treatment (Table 3). Association with baseline BMI and sex was revealed through multivariate logistic regression. Those of a normal weight (BMI =18-25) were nearly three times as likely to fail to reach a CD_4 cell count of 200 cells/µl by 12 months of treatment (AOR=2.82, 95% CI: 1.27-6.25), as compared to those with a BMI of ≤17 (underweight). Females were more than three times more likely to fail to attain 200 cells/µl by 12 months of treatment compared to males (AOR= 3.42, 95% CI: 1.53-7.59).

DISCUSSION

The study analysis reveals that CD_4 cell count recovery is a feasible tool for monitoring ART outcome in a resource limited setting like Ethiopia. In this study, CD_4 cell count recovers rapidly during the first six months of treatment, as evidenced by the six monthly median and mean changes. There was little subsequent change in median CD_4 cell count indicating that immune recovery was optimally achieved in the earlier phases of treatment. The

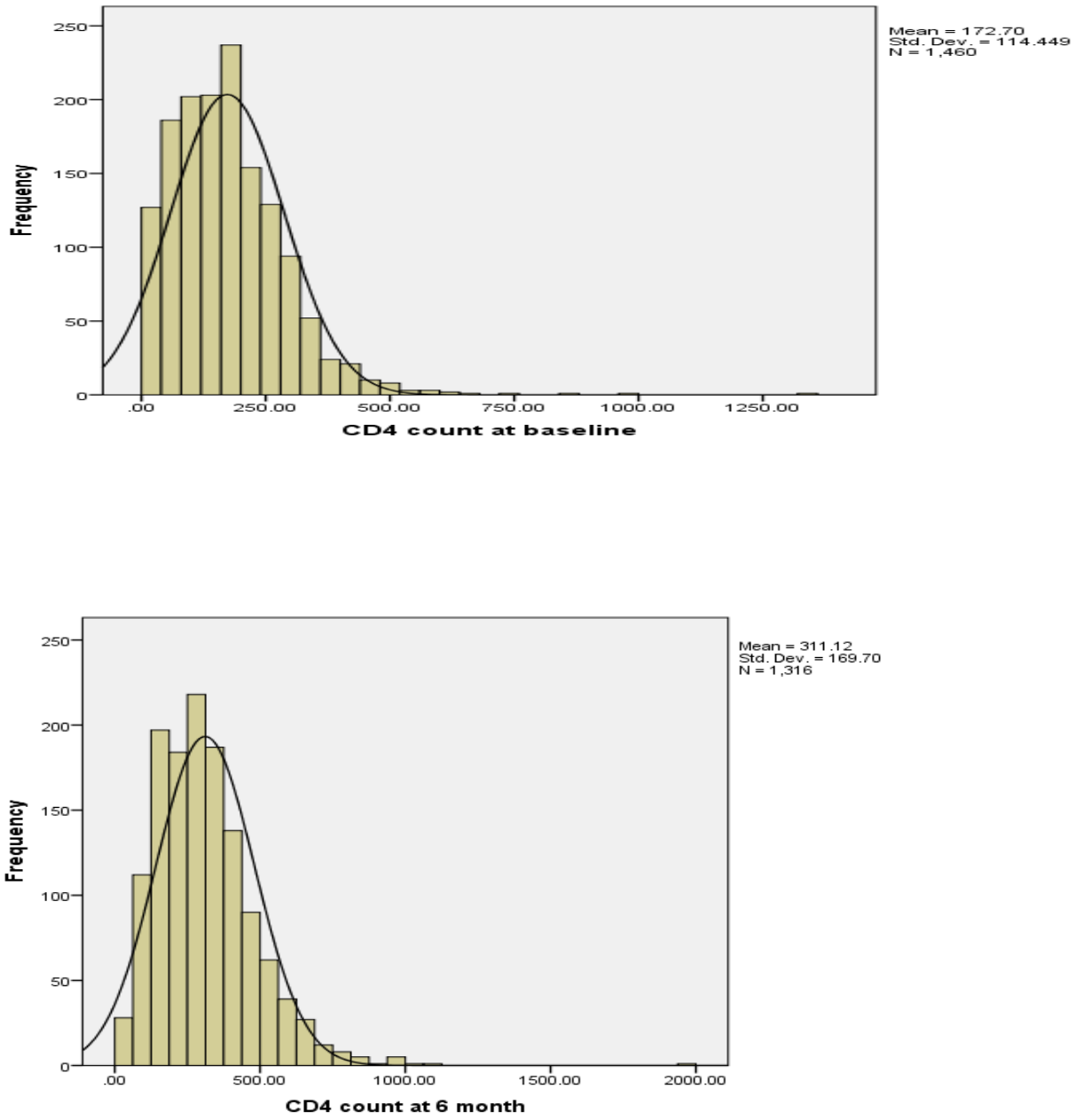

Figure 1. Graph showing absolute frequency distribution of CD_4 cell count (A) at baseline (n=1460) and (B) after 6 months of treatment (n=1316).

study observations corroborate similar studies that revealed that the most rapid and significant recovery of CD_4 cell count occurs during the first six months of treatment (Boulassel et al., 2012; Wright et al., 2011; Asfaw et al., 2015; Bennett et al., 2002).

A prospective study of South African patients revealed recovery is most rapid during the first 16 weeks months of treatment (Lawn et al., 2006). Thus, response in the early weeks and months of treatment is a robust predictor of ART treatment success, and adherence during early treatment is crucial for immunological recovery.

We observed steady and persistent CD_4 cell count recovery in those with baseline CD_4 cell counts of<200 cells/µl and 201 to 350 cells/µl (Figure 2). However,

Table 3. Predictors of CD_4 cell count response during ART. Responses are defined as (A) risk of immunological non-response (an increase of <50 cells/µl) or (B) failure to attain an absolute CD_4 cell count of ≥ 200 cells/µl following 12 months of treatment.

Variable		(A) Non response at one year (an increase of <50 cells/µl) at 12 month of treatment		(B) Failure to attain ≥200 cells/µl at 12 months of treatment (n=1140)	
		COR(95%CI)	AOR (95%CI)	COR(95%CI)	AOR (95%CI)
sex	Male	1	0.88(0.61-1.28)	1.00	1.00
	Female	1.14 (0.84-1.54)	1	3.68 (1.95-6.94)	3.42 (1.53-7.59)
Age category	Less than 25	1	1.68 (0.78-3.63)	1.00	1.00
	25-45	1.77 (0.95-3.30)	1.45 (0.85-2.50)	0.68 (0.20-2.32)	0.89 (0.23-3.53)
	>45	1.77 (1.12-2.80)	1	0.28 (0.07-1.11)	1.21 (0.23-6.40)
CDB category	<100	6.27 (2.98-13.160	5.17 (2.17-12.32)	-	-
	101-250	4.10 (2.03-8.27)	2.91 (1.29-6.53)	-	-
	251-350	3.41 (1.60-7.30)	2.80 (1.16-6.75)	-	-
	Greater than 351	1	1.00		
WHO stage	Stage I	1	1.04 (0.46-2.350	1.00	1.00
	Stage II	1.09 (0.63-1.90)	1.01 (0.52-1.96)	2.08 (0.46-9.39)	3.49 (0.47-25.98)
	Stage III	0.96 (0.58-1.570	0.79 (0.44-1.41)	1.25 (0.35-4.41)	2.96 (0.49-17.80)
	Stage IV	1.34 (0.69-2.60)	1.00	0.65 (0.17-2.55)	1.5 (0.21-10.43)
BMI category	Underweight	1	1.00 (0.30-4.24)	1.00	1.00
	Normal	1.01 (0.68-1.51)	1.10 (0.27-4.48)	2.19 (1.10-4.34)	2.82 (1.27-6.25)
	Overweight	1.05 (0.53-2.01)	1.38 (0.30-6.32)	3.41 (0.43-27.67)	6.88 (0.74-63.97)
	Obese	0.87 (0.23-3.32)	1.00	----	---
Regimen type	TDF+3TC+EFV	1	1.00 (0.60-1.70)	1.00	1.00
	TDF+3TC+NVP	1.10(0.61-1.96)	1.45 (0.67-3.12)	1.32 (0.27-6.49)	0.32 (0.05-2.14)
	AZT+3TC+EFV	0.71(0.45-1.00)	0.79 (0.42-1.47)	0.81 (0.33-2.00)	0.43 (0.13-1.43)
	AZT+3TC+NVP	1.54(0.91-2.60)	1.81 (0.88-3.70)	0.74 (0.31-1.77)	0.22 (0.06-0.77)
	D4T+3TC+EFV	1.37(0.84-2.20)	0.38 (0.69-2.63)	2.05 (0.79-5.34)	1.09 (0.28-4.17)
	D4T+3TC+NVP	0.93(0.92-2.95)	1.00	3.72 (1.25-11.13)	0.98 (0.26-3.770

recovery in patients with baseline CD_4 cell=351-500 cells/µl and CD_4 cell count >500 cells/µl fluctuated (rapid rise and fall). This fluctuation may be the result of this study small sample size for patients with baseline CD_4 cell count ≥351 cells/µl. Similar variation was observed in all subpopulations of similarly small sample size.

A high proportion of patients exhibited immunologic non-response (an increase of ≤50 cells/µl) at 12 months of treatment (19.3%), a proportion similar to that observed in a study conducted in Northern Ethiopia (22.7%) (Asfaw et al., 2015). Multivariate logistic regression revealed CD_4 cell count recovery was associated with baseline CD_4 cell count. Patients with low baseline CD_4 cell count exhibit greater non-response rates than those with higher baseline CD_4 cell count. A similar finding was observed in the EuroSIDA cohort study, where lower CD_4 count recovery was associated with lower rate of recovery (Florence et al., 2003). Some findings are in contrast to this study observations, in which lower response was associated with higher baseline CD_4 cell count (Lawn et al., 2006; Florence et al., 2003).

For those with a baseline CD_4 cell count of less than 200 cells/µl, failure to reach200cells/µl by 12months of treatment was associated with female gender, normal BMI (18 to 25) and D4T+3TC+NVP regimen. BMI was additionally significantly associated using a final multi-variate model. Patient with normal BMI (18 to 25) were three times more likely to fail to attain 200 cells/µl by 12 months of treatment than underweight patients. We observed a positive association between lower BMI and CD_4 cell. However, this association is inconsistently observed as evidenced from a study of a large sample size (n=8381) consisting of three cohorts. The study

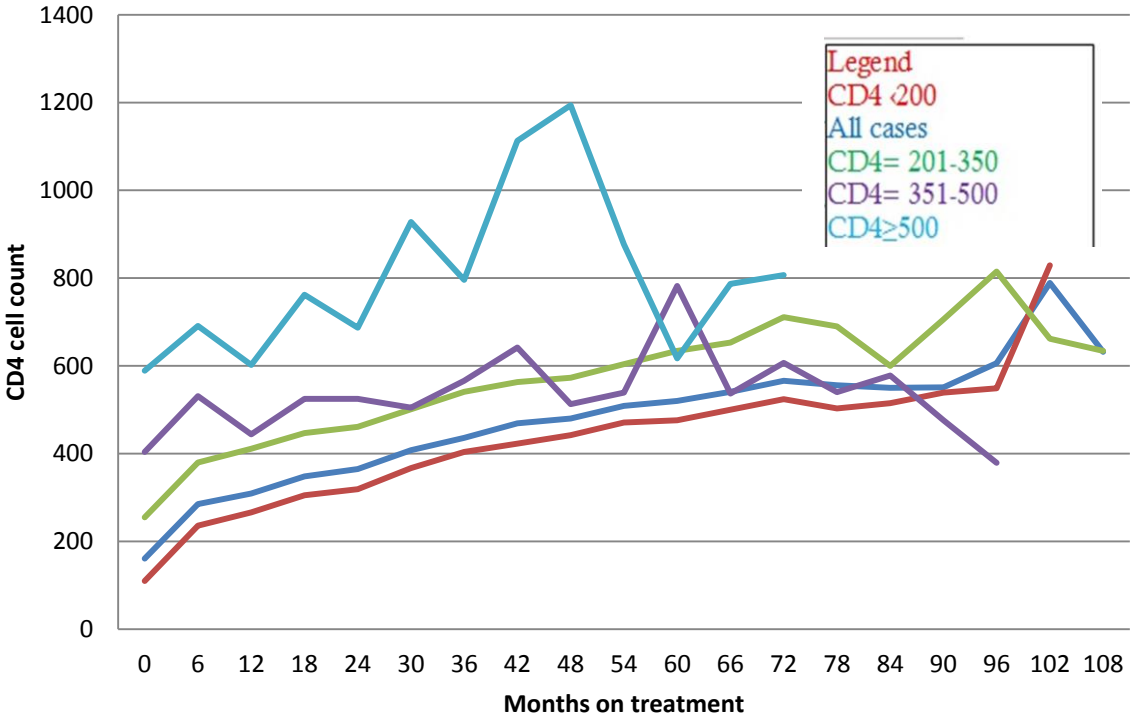

Figure 2. Graph showing six monthly median CD4 cell count changes for overall CD4 cell count, CD4 count less than 200 cells/ µl, CD4 cell count 201-350 cells/ µl, CD4 351-500 cells/ µl and CD4 count greater 500 cells/ µl.

concluded a BMI of approximately 30kg/m^2 at ART initiation was associated with greater CD_4 cell count recovery at 12 months compared with higher or lower BMI values (Koethe et al., 2015). These findings have no clear explanation yet. The study observed confidence interval for obese and overweight patients is likely due to the sample size.

In the study cohort we included all samples. Excluded populations were medical records of age less than 15 and which did not have baseline CD_4 cell count. Pediatrics have different treatment characteristics and differently treated from general population. Absence of baseline CD_4 cell count is unlikely to introduce sig-nificant bias. As a result, the internal validity of this paper is not significantly questionable. The findings of this study can be generalized to adult HIV-infected treatment-naïve patients in public health settings in Ethiopia, or even in other resource-constrained settings in Sub- Saharan Africa because of similar health service facility.

However, interpretation of these findings requires considering the limitations thereof. The limitations arise from the inherent characteristics of retrospective studies. We are unable to analyze important variables like mortality rate and adherence. The absence of these data might have affected the study estimation. Further prospective study designs are required to make confident conclusions.

In conclusion, we observed that recovery of CD_4 cell count is most rapid during the first six months of treatment. However, significant proportions of patients exhibit immunologic non-response. Patients with the lowest CD_4 counts in this setting have diminished capacity for immune recovery. These findings support the efficacy of ART in patients with a CD_4 cell count >500 cells/µl. Future prospective studies are required to corroborate the study observations regarding the long-term prospects for immune recovery among patients treated in ART programmes.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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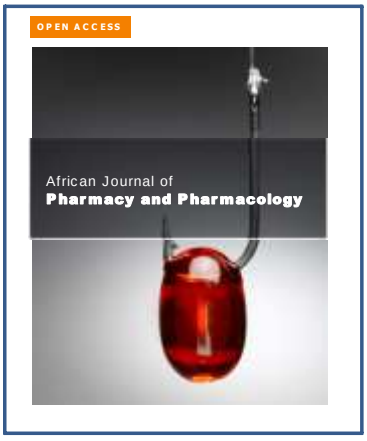

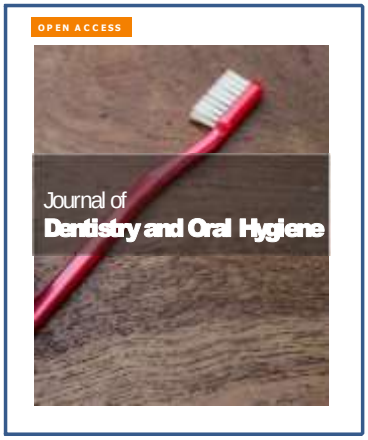

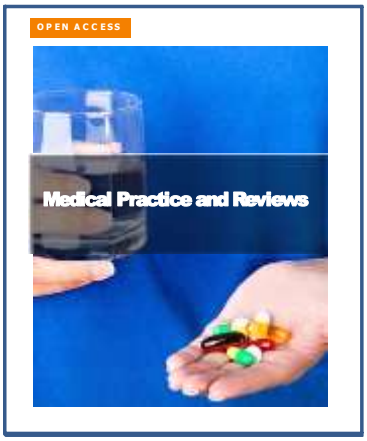

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