OPEN ACCESS

Journal of AIDS and HIV Research

April, 2018
ISSN 2141-2359
DOI: 10.5897/JAHR
www.academicjournals.org

ACADEMIC JOURNALS
expand your knowledge

ABOUT JAHR

The Journal of AIDS and HIV Research (JAHR) is published monthly (one volume per year) by Academic Journals.

Journal of AIDS and HIV Research (JAHR) is an open access journal that provides rapid publication (monthly) of articles in all areas of the subject like the implications for gender-based HIV and AIDS prevention interventions, Sputum cellularity in pulmonary tuberculosis, Comparative tolerability and efficacy of stavudine 30 mg versus stavudine 40 mg in patients on combination antiretroviral therapy, HIV and sexual risk behaviours amongst intravenous drug users etc.

The Journal welcomes the submission of manuscripts that meet the general criteria of significance and scientific excellence. Papers will be published shortly after acceptance. All articles published in JAHR are peerreviewed

Contact Us

Editorial Office: jahr@academicjournals.org

Help Desk: helpdesk@academicjournals.org

Website: http://www.academicjournals.org/journal/JAHR

Submit manuscript online http://ms.academicjournals.me/

Editors

Editorial Board

Journal of AIDS and HIV Research

Table of Contents: Volume 10 Number 4 April 2018

ARTICLES

academicJournals

Vol. 10(4), pp. 49-55, April 2018
DOI: 10.5897/JAHR2018.0459
Article Number: 3E8737856678
ISSN 2141-2359

http://www.academicjournals.org/JAHR

Journal of AIDS and HIV Research

Full Length Research Paper

Survival time of human immunodeficiency virus (HIV) infected children under 15 years of age after initiation of antiretroviral therapy in the University of Gondar Comprehensive Specialized Hospital, Ethiopia

Asrat Atsedeweyn Andargie[1*] and Yemane Asmleash[2]

[1]Department of Epidemiology and Biostatistics, Institute of Public Health, College of Medicine and Health Sciences, University of Gondar, Ethiopia.
[2]Department of Statistics, Collage of Natural and Computational Sciences, Aksum University, Aksum, Ethiopia.

Received 20 February, 2018; Accepted 13 March, 2018

Human immunodeficiency virus (HIV) has emerged as one of the leading causes of childhood mortality and morbidity in sub Saharan Africa. But, the attention given to HIV-infected children in terms of providing antiretroviral treatment (ART) had so far been ranked second. The study had the objectives of identifying predictors that had significant impacts on the survival status of HIV infected children who received antiretroviral treatment care in the University of Gondar Comprehensive Specialized Hospital, Gondar, Ethiopia. The data used in the study was based on secondary data from hospital records of HIV infected children aged below 15 years who started ART between 2008 and 2013 and who followed through April 2015 in University of Gondar Comprehensive Specialized Hospital, Gondar, Ethiopia. The Multivariable Cox Proportional model was fitted to identify factors affecting the survival of children after initiation of ART. The median survival time frame was found to be 55 months. At the end of the follow up, 46 (17.1%) children died due to the disease, the remaining 223 (82.9%) were alive and lost to follow-up. The multivariate analysis of the Cox Regression model showed that the age of a patients (for age < 1.5 years HR: 3.590 ; 95% CI: 1.439, 8.953; P = 0.006, baseline hemoglobin level (for hemoglobin level < 7g/dl HR: 6.286; 95% CI: 2.328, 16.973; P=0.000, WHO clinical stage (For stage III HR: 0.308 ; 95% CI: 0.150, 0.630; P = 0.001); and baseline CD4 count(HR: 0.180 ; 95% CI: 0.084, 0.388; P = 0.000) are significant factors of survival of HIV infected children during the 92 months of follow up. Therefore, special attention should be given to younger children in ART; patients with low CD4 cell count, patients with advanced WHO clinical staging (stage III and IV); and patients with low hemoglobin level to improve the survival of HIV infected children treated with ART.

Key words: Children, antiretroviral therapy (ART), HIV, survival, Ethiopia.

INTRODUCTION

The occurrence of the acquired immunodeficiency syndrome (AIDS) epidemic is amongst the forefront public health challenges that the world has faced (UNAIDS The Gap Report, 2014). It has had some strong emotional effects on individuals and families with the implications of untimely death along with medical, financial and social burdens for the past three decades. Millions of people have died of the human

immunodeficiency virus (HIV) infection.

Globally, an estimated 35 million (33.2 million to 37.2 million) people were living with HIV in 2013 (Newell et al., 2004). In sub-Saharan Africa, the number of AIDS-related deaths fell by 39% between 2005 and 2013. The region still accounted for 74% of all the people dying from AIDS-related causes in 2013 (UNAIDS The Gap Report, 2014). There are 2.9 million (2.6 million to 3.2 million) children (aged 0 to 14) living with HIV in sub-Saharan Africa. Of the estimated 1.8 million people living with HIV, 1.5 million were living in this region. There were also 190,000 child deaths of AIDS-related illnesses during 2013, out of 1.5 million people overall (WHO, 2014). Ethiopia is one of the sub-Saharan African countries hardly-hit by HIV/AIDS in all of its manifestations. In 2013, there were an estimated 793,700 (716,300-893,200) people living with HIV including 200,300 (172,400 to 232,400) children according to the EPP/Spectrum modelling (UNAIDS, 2014 EPP/Spectrum).

Tremendous progress has been made over the past few years in diagnosing and treating infants and children with HIV infection. However, much remains to be done to effectively scale up and sustain prevention efforts and treatment services for all in need. Treatment of HIV-infected children with Antiretroviral Therapy (ART) leads to immune reconstitution which results in an increase in CD4 lymphocyte counts, decreased risk of opportunistic infection and improved survival (UNAIDS The Gap Report, 2014; Newell et al., 2004).

Moreover, children may die with an undetectable viral load and inadequate CD4 count recovery (Estimation and Project Package for HIV, 2014). However, very little attention has been given to how other factors, not relating to ART drugs, may influence the survival of HIV infected children. Therefore, this research is undertaken to explore the factors that have strong association with the survival experience of HIV-infected children treated with ART in the University of Gondar Comprehensive Specialized Hospital.

The study had the objectives to assess the relationship of explanatory variables to survival time, estimate the survival duration and identify predictors that have significant impacts on the survival status of HIV infected children who received Antiretroviral Treatment and care in the University of Gondar Comprehensive Specialized Hospital, Gondar, Ethiopia.

METHODOLOGY

Study area, design, and period

The data for the study were obtained from patients' ART follow up records. During the study period, from the HIV cohort database, a total of 756 children were recorded. However, only 269 patients with a full record of variables who started ART between 2008 and 2013 were included and continued until April 2015 in the University of Gondar Comprehensive Specialized Hospital. The data were collected based on the child's identification number in HIV cohort database without any direct contact with a child so as to maintain the confidentiality of the child's record. Demographic data, laboratory and clinical information of all children aged <15 years who started ART were included.

Variables of the study

The study focused only on demographic variables (age, and gender) and clinical/immunological variables (baseline weight, WHO Clinical Stage, Prophylaxis taken, baseline functional status, Baseline TB status, Reason for taking ART, baseline CD4 count, baseline hemoglobin levels, Opportunistic Illness) that can affect the survival time of HIV-infected children. The response variable in the study is the survival time of HIV-infected children measured in months after starting ART. This was measured according to the time a child had follow up from the time the child began to receive treatment until the time of an event (death) or lost to follow up (for those right censored subjects).

Operational definitions

(1) CD4 count is one of the factors used to determine when to start antiretroviral therapy (ART).
(2) Threshold CD4 count: The CD4 cell count of a person who does not have HIV can be anything between 500 and 1500. People living with HIV who have a CD4 count over 500 are usually in pretty good health.

Statistical model

A variety of models and methods have been developed for doing this sort of survival analysis using either parametric or semi-parametric approaches. One of the most popular types of regression models used in survival analysis is the Cox Proportional Hazard Model (Cox, D.R. Regression models and life Tables (with Discussion), 1972). The Cox Regression Model is used to determine which combinations of explanatory variables affect the form of the hazard function. Also the model is used to obtain an estimate of the hazard function for an individual who may be of interest. The Cox Regression Model can be used for data that contains censored observations. The model also takes into account the fact that the probability of experiencing an event differs with duration of exposure to risk. In particular we apply the semi-parametric Cox proportional hazard model because it is the most commonly used model in hazard regression.

RESULTS

A total of 269 participants with full record of variables were included in the study. From this number, 46 (17.1%)

*Corresponding author. E-mail: asrat07@gmail.com

Table 1. Distribution of important socio-demographic and health factors of HIV infected children.

Covariates	Category	Censored (%)	Dead	Total
Age	Age less than 1.5 years	19 (67.9%)	19	28
	Ages between 1.5-5 years	75 (78.1%)	21	96
	Ages between 5 - 14 years (the reference category)	129 (89.0%)	16	145
Gender	Male	92 (79.3%)	24	116
	Female	131(85.6%)	22	153
Baseline functional status	Working	124 (87.3%)	18	142
	Ambulatory	58 (85.3%)	10	68
	Bedridden	41 (69.5%)	18	59
Baseline WHO stage	Stage 1	44 (95.7%)	2	46
	Stage 2	59 (95.2%)	3	62
	Stage 3	72 (86.7%)	11	83
	Stage 4	48 (61.5%)	30	78
Baseline CD4 count	Above the threshold	120(93.0%)	9	129
	Below the threshold	103(73.6%)	37	140
Original regimen	D4T-3TC-NVP	85 (81.7%)	19	104
	D4T-3TC-EFV	8 (72.7%)	3	11
	AZT-3TC-NVP	102 (84.3%)	19	121
	AZT-3TC-EFV	9 (75.0%)	3	12
	Other drugs	19 (90.5%)	2	21
Reason For ART	Clinical	20 (87.0%)	3	23
	CD4	87 (77.7%)	25	112
	CD4 and clinical	80 (90.9%)	8	88
	CD4 and lymphocytes	36 (78.3%)	10	46
Continuous Prophylaxis use	No	68 (85.0%)	12	80
	Yes	155 (82.0%)	34	189
Baseline TB Screen	- ve	108 (84.4%)	20	128
	+ve	115 (81.6%)	26	141
Opportunistic Illness	No	102 (82.3%)	22	124
	Yes	121(83.4%)	24	145
Base line hemoglobin level (gm/dl)	≤7.00 gm/dl	76 (78.4%)	21	97
	7.00 to 8.50 gm/ dl	30 (73.2%)	11	41
	8.50 to10.00 gm/dl	43 (82.7%)	9	52
	> 10.00 gm/dl (reference category)	74 (93.7%)	5	79

children died due to the disease, 223 (82.9%) were alive or loss to follow-up during the time of data collection. Out of the total 269 ART patients, 116 (36.65%) were male and the remaining were females. Among the 269 children, 78 (30%) were at clinical stage IV, 82 (30.5%) were at clinical stage III, 63 (23.4%) were at clinical stage II and the rest which amount to 46 (17.1%) children were at clinical stage I when they started ART (Table 1).

From the results of the Multivariate analysis using the significant variables found in Table 2, the covariates age, WHO clinical stages, CD4 counts and hemoglobin level are the four categorical variables that are found to be

Table 2. Multivariate analysis using the significant variables in the equation.

Variable	B	SE	Wald	df	Sig.	Exp (B)	95.0% CI for Exp (B)	
							Lower	Upper
Age	-	-	11.257	2	0.004	-	-	-
Age(1)	1.278	0.466	7.513	1	0.006	3.590	1.439	8.953
Age(2)	0.968	0.341	8.077	1	0.004	2.632	1.350	5.130
Baseline WHO stage	-	-	24.502	3	0.000	-	-	-
Baseline WHO stage (1)	-2.443	0.744	10.794	1	0.001	0.087	0.020	0.373
Baseline WHO stage (2)	-1.890	0.623	9.192	1	0.002	0.151	0.045	0.513
Baseline WHO stage (3)	-1.179	0.366	10.370	1	0.001	0.308	0.150	0.630
Baseline CD4 count	-1.713	0.391	19.200	1	0.000	0.180	0.084	0.388
Baseline hemoglobin	-	-	13.658	3	0.003	-	-	-
Baseline hemoglobin (1)	1.838	0.507	13.158	1	0.000	6.286	2.328	16.973
Baseline hemoglobin (2)	1.721	0.550	9.795	1	0.002	5.592	1.903	16.436
Baseline hemoglobin (3)	1.633	0.600	7.406	1	0.007	5.119	1.579	16.593

significantly associated with the survival time of HIV infected children under ATR treatment in the fitted Cox regression model.

Let us begin with Baseline CD4 cell count of the patient that is supposed to be significant both clinically and statistically. In this study, a Baseline CD4 cell count has been found to have a significant impact on the survival time of HIV infected children. The estimated hazard ratio for baseline CD4 counts is 0.180 (with a 95% C.I. 0.084 to 0.388). Thus, patients whose CD4 counts are above the threshold levels have an 82% lower risk of death than those whose CD4 counts are below the threshold levels. The confidence interval indicated that the risk of death for those patients that have CD4 counts above the threshold levels could be lower by 38.8% or as low as 8.4% than patients that have CD4 counts below the threshold levels (500 cells/mm^3); $p < 0.0001$.

HIV-infected children aged below 1.5 years are 3.59 times more likely to die than children aged between 5 to 14 years. The 95% C.I. confirmed that the hazard of death for this category could be as low as 1.439 and as high as 8.953 compared with children aged between 5 to 14 years. HIV-infected children aged between 1.55 and 5 years are 2.632 times more likely to die than children between the ages of 5 to 14 years. The 95% CI verified that the rate of death could be as small as 1.350 and as large as 5.130. HIV-infected children aged below 1.5 years are 1.36 times more likely to die than HIV-infected children aged between 1.5 and 5 years given that all other factors are constant.

The estimated risks of death for a patient with hemoglobin levels less than 7gm/dl as compared to those patients with hemoglobin levels greater than 10gm/dl (reference category) are 6.286 (95% CI: 2.323, 16.973). This means that the hazard rate of death of a child for a hemoglobin level less than 7gm/dl is 6.286 times more likely to die than HIV-infected children with hemoglobin level greater than 10gm/dl. In addition, the estimated relative risk (hazard ratio) of dying patients with hemoglobin levels between 7 to 8.5gm/dl are 5.592 times more likely to die as compared to those patients with hemoglobin level greater than 10gm/dl(reference category).

The 95% C.I. suggests that the rate of death could be as low as 1.903 and as high as 16.436. Moreover, the estimated hazard ratio of hemoglobin levels between 8.5 to 10gm/dl compared to the reference hemoglobin level is 5.119 (95% CI: 1.579, 16.593). This implies that the risk of dying for patients with hemoglobin levels between 8.5 to 10gm/dl is 5.119 times more likely to die than those patients with hemoglobin levels greater than 10gm/dl (reference category). Children with hemoglobin levels less than 7gm/dl are 1.124 times more likely to die than children with hemoglobin levels between 7gm/dl to 8.5gm/dl. Moreover, children with hemoglobin levels greater than 10gm/dl are 84% less likely to die than children with hemoglobin value less than 7gm/dl provided that all other factors are held constant.

The reference category for the design variables of WHO clinical stage is patients who are in the specified WHO clinical stage IV. The estimated hazard ratio for clinical stage III is 0.308 (with a 95% C.I. 0.15-0.630). Thus, the hazard of death for clinical stage III is 70% less likely than those of clinical stage IV. On the other hand, the estimated hazard ratio of stage III compared to stage II was 2.04 $= exp(-1.179 - (-1.890))$. Since the confidence interval does not contain 1, an individual in clinical stage III has a significantly higher hazard rate than patients in clinical stage II. Thus, patients in stage III are 2.04 times more likely to die than patients in stage II.

Assessing the goodness of fit of the model

The goodness of fit of the proportional hazard model was checked based on the empirical data. Therefore, for the

Table 3. Likelihood ratio, score and wald tests for testing the global null hypothesis of $\boldsymbol{\beta} = \mathbf{0}$. Testing global null hypothesis: $\boldsymbol{\beta} = \mathbf{0}$

Test	Chi-Square	Df	Pr>Chisq
Likelihood ratio	78.647	9	<0.0001
Score	74.786	9	<0.0001
Wald	67.759	9	<0.0001

Moreover, Cox-Snell residuals are used to assess the overall goodness of fit of the model.

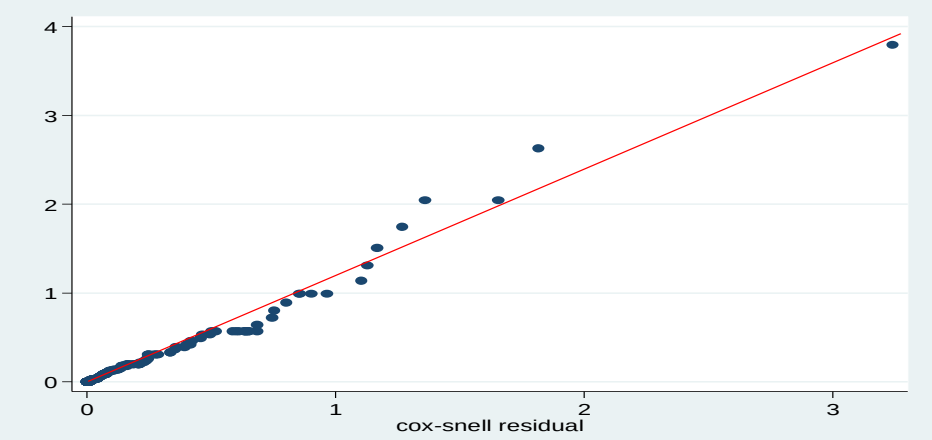


Figure 1. Cumulative hazard plot of the Cox-Snell residuals of the cox proportional hazards regression model.

model fitted in this study, the Likelihood Ratio, Score and Wald tests were used to compare (at 5% significance level) the goodness of fit of the model. The SAS output in Table 3 revealed that the log partial likelihood function *(-2LL)* without covariate was 489.281 while the function with significant covariates was 410.634. This result showed that the model is appropriate with a chi-square of 78.647 with 9 degrees of freedom and a p-value of <0.0001. The plot in Figure 1 of the cumulative hazard function of the Cox-Snell residual against the Cox-Snell residuals are fairly close to the 45° straight line through the origin. This suggested that the model fit to the data is satisfactory. The 45^0straight line through the origin is drawn for reference.

DISCUSSION

This study identified variables/factors that are significantly associated with survival time of HIV-infected children under ART treatment. The results of this study showed that the risk of death among HIV infected children among the age groups of less than 1.5 years and 1.5 to 5 years are higher than those ages between 5 to 14 years. A study by Gebremedhin et al. (2013) identified independent predictors of children's mortality on ART. The result suggested that the mortality of children on ART was low and factors that affect mortality of children on ART were among those children who were less than 18 months of age.

A similar study by Munyagwa et al. (2012) also found that mortality among HIV-infected children was highest among those aged less than 2 years. Thus, mortality among these high risk groups contributed to the higher rate of mortality. CD4 cell count is the most important marker of HIV disease progression and a strong predictor of the survival of HIV-infected children, similar to the plasma viral load. That may be due to the fact that HIV attacks CD4 cells, and as time elapses people with HIV often notice their CD4 cell counts drop. Hence, the lower the CD4 cell count the greater the chances of acquiring a number of very serious diseases. The significant impact of CD4 cell counts on patients' survival rate has been acknowledged by many studies.

A study by Brady et al. (2010), Lumbiganon et al. (2011) and Phongsamart et al. (2013) reported that HIV-infected children with low baseline CD4 cell counts had a strong likelihood of early mortality. The results in this current study are also consistent with the findings in the above studies. But, a similar study conducted by

(Habtamu and Eshetu, 2012) in Bahir-Dar found that low baseline CD4 cell counts was not a predictor of survival time of HIV infected children. His finding contradicts our findings that a low baseline CD4 cell counts were a strong risk factor for survival time of HIV infected children.

The finding of this study observed that a higher risk of mortality was found among HIV-infected children with lower hemoglobin levels (anemic groups) compared to hemoglobin levels greater than 10gm/dl. This study was consistent with other studies conducted elsewhere. According to Ebissa et al. (2015), it was found that hemoglobin levels less than 7 gm/dl were significant independent predictors of death after controlling for other factors. For instance, another study also identified that the determinants of mortality in Bahir Dar showed that the risk of death is higher among HIV-infected children with a lower hemoglobin level [13]. Therefore, the above studies confirm the same conclusion as ours.

Like CD4 cell counts, the WHO Clinical Staging system has been shown to be a practical and accurate way to manage HIV-infected patients. In this study, we found that the advanced WHO clinical stages III and IV were independent markers of mortality for patients on ART. The possible justification for the finding is that the advanced clinical stage of the disease is the cause for HIV-associated complications. A study in Lumbiganon et al. (2011) found that those children with WHO clinical stage IV had an increased risk of death. Similar to our findings, studies by Atnafu et al. (2012), Ebissa et al. (2015) and Adem et al. (2014) provided evidence that HIV infected children on ART in advanced clinical stages (III and IV) had a strong association with high mortality.

The aforementioned sources showed that the most significant predictors of survival of children were CD4 count, advanced WHO clinical stages, age, weight and to some extent opportunistic diseases like anemia and pneumonia. The findings of the current study identified and focused on advanced WHO clinical stage, age, hemoglobin level and baseline CD4 count as determinant predictors of survival of HIV-infected children who were treated with ART at the University of Gondar Comprehensive Specialized Hospital. Weight did not come out as a strong predictor although it is a clinically meaningful determining variable.

Conclusions

In this study, we tried to identify the factors that are associated with survival time of HIV infected children treated with ART in the University of Gondar Comprehensive Specialized Hospital using the methods of survival analysis. The Kaplan-Meier and log-rank test are used to estimate and compare the survival time of children after initiation of ART treatment. The study has shown that the overall median survival time of HIV infected children under the study was 51.1 months. During the follow-up period, out of the 269 HIV infected children 46 (17.1%) of them experienced the event (that is, death).

Moreover, the results of the multivariable proportional hazards Cox regression model showed that CD4 count at the start of ART, age, advanced WHO clinical stages and low hemoglobin level (less than 7gm/dl and between 7 to 8.5gm/dl) are associated with a higher risk of mortality. And also HIV- infected children at ages less than 1.5 years and ages between 1.5 to 5 years and who were at advanced WHO clinical stage III & IV are also associated with increased rate of mortality in both the univariable and multivariable analysis. Similarly, patients with poor health indicators like low baseline CD4 cell counts and low hemoglobin levels are less likely to survive.

Therefore, special attention should be given to younger children in ART; children should start ART treatment at an early age, with CD4 cell counts at the normal level or above the threshold level and when they have higher hemoglobin values and when they are at a lower clinical stage.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ACKNOWLEDGEMENTS

The authors appreciate the support of the University of Gondar Comprehensive Specialized Hospital staff members for dedicating their time in providing the necessary data.

REFERENCES

Adem AK, Alem D, Girmatsion F (2014). Factors affecting survival of HIV positive children taking antiretroviral therapy at Adama Referral Hospital and Medical College, Ethiopia. J. AIDS Clin. Res. 5(3):289.

Atnafu H, Wencheko E (2012). Factors affecting the survival of HIV-infected children after ART initiation in Bahir-Dar, Ethiopia. Ethiop. J. Health Dev. 26(3):193-199.

Brady MT, Oleske JM, Williams PL, Elgie C, Mofenson LM, Dankner WM, Van Dyke RB (2010). Declines in Mortality Rates and Changes in Causes of Death in HIV-1-Infected Children during the HAART Era. J. Acquir. Immune Defic. Syndr. 53(1):86-94.

Cox DR (1972). Regression Models and Life-Tables (with Discussion). J. R. Stat. Soc. Series B (Methodological) 34(2):187-220.

Ebissa G, Deyessa N, Biadgilign S (2015). Predictors of early mortality in a cohort of HIV-infected children receiving high active antiretroviral treatment in public hospitals in Ethiopia. AIDS Care 27(6):723-730.

Federal Democratic Republic of Ethiopia (2014). Country Progress Report on the HIV response. 2014. Available at: http://www.unaids.org/sites/default/files/country/documents/ETH_narrative_report_2014.pdf

Gebremedhin A, Gebremariam S, Haile F, Weldearegawi B, Decotelli C (2013). Predictors of mortality among HIV infected children on anti-Health 13(1):1047.

Habtamu A, Eshetu W (2012). Factors affecting the survival of HIV-infected children after ART initiation in Bahir-Dar, Ethiopia. Ethiop. J. Health Dev. 26(3):193-199.

Lumbiganon P, Kariminia A, Aurpibul L, Hansudewechakul R, Puthanakit T, Kurniati N, Kumarasamy N, Chokephaibulkit K, Nik Yusoff NK, Vonthanak S, Moy FS, Razali KA, Nallusamy R, Sohn AH (2011). Survival of HIV-infected children: a cohort study from the Asia-Pacific region. J. Acquir. Immune Defic. Syndr. 56(4):365-371.

Munyagwa M, Baisley K, Levin J, Brian M, Grosskurth H, Maher D (2012). Mortality of HIV-infected and uninfected children in a longitudinal cohort in rural south-west Uganda. Trop. Med. Int. Health 17(7):836-843.

Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F (2004). Mortality of infected and uninfected infants born to HIV-infected mothers in Africa. Lancet 364(9441):1236-1243.

Phongsamart W, Hansudewechakul R, Bunupuradah T, Klinbuayaem V, Teeraananchai S, Prasithsirikul W, Kerr SJ, Akarathum N, Denjunta S, Ananworanich J, Chokephaibulkit K (2013). Long-term outcomes of HIV-infected children in Thailand. Int. J. Infect. Dis. 22:19-24.

retroviral therapy in Mekelle Hospital, Northern Ethiopia. BMC Public

United Nations Programme on HIV/AIDS (UNAIDS) (2014). Strengthening HIV Estimates: EPP/Spectrum 2015. Report and recommendations from a meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections, Geneva, Switzerland, 27-29 October 2014. Available at: http://www.epidem.org/sites/default/files/reports/Geneva%20report_FINAL_0.pdf

United Nations Programme on HIV/AIDS (UNAIDS) Gap Report (2014). The Gap Report, 2014. Available at: http://www.unaids.org/en/resources/documents/2014/20140716_UNAIDS_gap_report

World Health Organization (WHO) (2014). WHO report in partnership with UNICEF and UNAIDS. Global update on the health sector response to HIV, 2014. Available at: http://www.who.int/hiv/pub/progressreports/update2014/en/

academicJournals

Vol. 10(4), pp. 56-63, April 2018
DOI: 10.5897/JAHR2018.0457
Article Number: FD0C94F56680
ISSN 2141-2359

http://www.academicjournals.org/JAHR

Journal of AIDS and HIV Research

Full Length Research Paper

A prospective study on the changes of clinical values in HIV-Infected patients attending Kenyatta National Hospital Comprehensive Care Center

Jackson Ireri Mrama[1*], Ngeranwa, J. N.[1], Mburu, D. N.[1], Jaoko, W.[2] and Sekadde-Kigondu C.B.[3]

[1]Department of Biochemistry and Biotechnology, Kenyatta University, Nairobi, Kenya.
[2]Department of Medical Microbiology, University of Nairobi, Kenya.
[3]Department of Human Pathology, University of Nairobi, Kenya.

Received 9 January, 2018; Accepted 1 March, 2018

Changes in serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (G-GT), total protein (TP), albumin (ALB), total bilirubin (T. Bil), direct bilirubin (D. Bil) are assayed to monitor liver function; while those of creatinine (CRT) and urea (UR) are for kidney functions. These two organs produce hepcidin and erythropoietins, respectively that play major roles in haemopoiesis and so may be involved in HIV- associated anemia. Anemia occurs in over 70% of HIV-infected. The objective of this study was to monitor liver and kidney derangements in HIV based on CD4+ cell levels for 6 months. This was a longitudinal descriptive study conducted at Kenyatta National Hospital Comprehensive Care Centre and involved: 184 HIV seropositive and 101 HIV seronegative blood donors as a comparative group. The comparative group demonstrated significantly higher T.Bil and D.Bil mean values in males than in females. Increases in each of: G-GT, T. Bil, D. Bil, AST, ALT and CRT above the upper limit of the control were observed. Increases in G-GT were highest in CD4+ above 200 cells /mm3; decreases in the levels of ALP and ALB were lowest in CD4+ < 200 cells / mm3 group. Increases in G-GT with decreases in ALP were possibly due to cardiac-related disorders. Serum levels of AST, ALT and CRT are not affected by CD4+ levels. Decreases in the levels of ALB in CD4+ < 200 cells/mm3 group were thought to be partly due to: anemia, malnutrition or hypercatabolism. Hypoalbuminemia may result in altered albumin: globulin ratio. Determinations of: albumin: globulin ratio, gender-based reference ranges for T. Bil and D. Bil, hepcidin and erythropoietin are recommended.

Key words: Study, clinical values, HIV infection.

INTRODUCTION

Biochemical parameters are routinely evaluated in the laboratory to detect liver and kidney derangements. These two organs play a major role in erythropoiesis by anemia development. Anemia is the commonest hematological abnormality in immunodeficiency virus (HIV) infection with as many as 70 - 80% of the patients producing hepcidin and erythropoietin respectively (Ganz and Nemeth, 2012; Amanzada et al., 2011; Beverborg et al., 2015). Inefficiencies of these organs will be key to developing anemia in the course of infection frequently complicating advanced HIV infection. For liver function assessment serum levels of: aspartate aminotransferase,

alanine aminotransferase, alkaline phosphatase, gamma - glutamyl transferase, total protein, albumin, total bilirubin and direct bilirubin are determined. Liver disease is the most common non-AIDS related cause of death among HIV-infected patients, accounting for 14-18% of all deaths and up to 90% of patients with AIDS have had abnormalities of the liver-associated enzymes (Poles et al., 1997). Increases in ALT and AST is indicative of hepatocellular injury (Mata-Marin et al., 2009; Clark et al., 2003). A rise in the levels of both ALP and GGT indicate cholestatic disease (Patil et al., 2013). Elevation of ALP occurs as a result of obstructed bile flow of either the intra - hepatic or extra - hepatic biliary tree (Patil et al., 2013). Serum levels of GGT is associated with morbidity, including cardiovascular disease independent of liver disease or alcohol consumption (Rahman et al., 2014; Jiang et al., 2013). Decreased levels of ALB have been reported in HIV infected antiretroviral therapy (ART)-naïve patients (Dusingize et al., 2015). Albumin is a measure of hepatic synthetic function with albumin levels decreased in chronic liver disease (Limdi and Hyde, 2003). It has been previously reported that both hypoalbuminemia and hyperproteinemia are associated with a polyclonal gamma-globulinemia in HIV seropositive patients (Hunziker et al., 2003). Bilirubin, a yellow compound arising from haem iron, is used either to monitor for toxicity to ARV or assess liver function where viral hepatitis is a co-infection. Kidney functional state is assessed by measuring serum levels of urea and creatinine. Kidney disease has been reported as an important complication of human immunodeficiency virus (HIV) infection that may be associated with progressing to AIDS and death (Agbaji et al., 2011; Scarpino et al., 2015). Many reports of the biochemical changes in HIV infection are derived from populations in industrialized nations.

In this study changes in clinical parameters were done to evaluate liver and kidney derangements in HIV – infected adults grouped into CD4+ cell counts of: < 200 -, 200-499 - and ≥ 500 cells/mm^3 over six months' period.

MATERIALS AND METHODS

The study protocol was approved by Kenyatta National Hospital/ University of Nairobi (KNH/UoN) ethics and research committee. The study was conducted between 2013 and 2016 period and the study population was comprised of: HIV seropositive subjects on various ARV regimens for periods exceeding six months, HIV ARV – naïve subjects and HIV seronegative blood donors (comparative group). In total the subjects were 184 and the blood donors were 101. All the participants were adults aged between 18 and 60 years and were recruited consecutively as they consented. Clinical and social demographic characteristics of the study participants were recorded. The study subjects were grouped into CD4+ < 200 (n = 22) -, 200-499 (n = 86) – and ≥ 500 (n = 76) cells/mm^3 groups based on the CD4+ counts in the blood sample at recruitment. The CD4+ groups were further grouped into males and females: CD4+ < 200 (13 males and 9 females) -, 200-499 (43 males and 43 females) - and ≥ 500 (9 males and 67 females) cells/mm^3 groups. A total of 5 ml of blood samples were obtained from each study subject at recruitment (F_0), after 3 months (F_1) and after 6 months (F_2) during the study; while blood sample were obtained from the comparative group at the recruitment stage only. The blood samples were assigned study numbers, divided into two milliliters and three milliliters portions and dispensed into EDTA vacutainers and plain tubes respectively. The EDTA samples were used for CD4+ cell counts; while sera from blood samples in plain vacutainers were used for: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma - glutamyl transferase (G-GT), total protein (TP), albumin (ALB), total bilirubin (T. Bil), direct bilirubin (D. Bil), creatinine (CRT) and urea (UR). The CD4+ counts were done on a FACS CALIBUR® machine that used commercial controls set at zero, low, medium and high concentrations for quality control. Biochemistry parameters were measured using a fully automated HUMASTAR: 600 ® analyzer using normal and pathological commercial controls for quality control. The reagents employed for the analyses were Human ® products from Germany procured through the local agent, CEM LABs limited. Parameters whose mean demonstrated significant differences after comparing male and female mean values in the comparative group, were also analyzed under males and females separately in HIV seropositive respondents. The results of the tests were recorded as raw data in laboratory note book, entered into excel computer data base then after cleaning and verification transported into statistical package for the social sciences (SPSS) version 21 and analysis done there-in. Means, standard error of the mean, minimum and maximum ranges were determined. Comparison of the means between males and females; between HIV negative and HIV positive respondents was done using student - t test. HIV negative respondents' 95% confidence interval (C.I) was used as reference ranges to determine increased or decreased parameters of HIV positive respondents.

RESULTS

Demographic characteristics of the respondents are presented in Table 1. For the comparative group, the mean age was 30.2 years, 74.3% were male, 63.4% had tertiary education, 45.5% were students, 95% were non-smokers and 75.2% did not consume alcohol. For the HIV positive group, the mean age was 39.7, 64.7% were females, 43.5% had secondary education, 51.1% were employed, 98.9 % were non-smokers and 88% were teetotaler. The CD4+ cell levels for all the respondents were determined at the commencement of the study and also on the third and sixth months, for the HIV infected individuals. Baseline data indicated that the CD4+ counts for the HIV negative control group averaged 780.9 ±31.2 cells /mm^3 while that of the HIV positive individuals was

*Corresponding author. E-mail: jacksonirerimrama@gmail.com.

Table 1. Demographic characteristics of the respondents.

Variable	HIV-Infected				HIV-Negative (Referents)			
	Mean±SEM	Min-Max	F (%); N=184	95% CI	Mean±SEM	Min-Max	F (%); N=101	95% CI
Age (Year)	39.7±0.63	19-59		26.1-53.3	30.2±0.96	18-56		28.3-32.1
Education								
None	-	-	1 (0.5)	12.3-22.9	-	-	1 (1)	0.2-5.3
Primary	-	-	41 (22.3)	17.8-29.8	-	-	10 (9.9)	3.4-17.1
Secondary	-	-	80 (43.5)	36-50	-	-	26 (25.7)	18.9-35.8
Tertiary	-	-	62 (33.7)	27-40.3	-	-	64 (63.4)	54.7-72.9
Occupation								
None	-	-	0 (0)	0.1-2.0	-	-	1 (1)	1.2-5.3
House wife	-	-	10 (5.4)	2.9-9.5	-	-	0 (0)	0.2-5.3
Business	-	-	76 (41.3)	37-51	-	-	24 (23.8)	15.2-32.3
Employed	-	-	94 (51.1)	42.7-56.8	-	-	30 (29.7)	22.1-39.1
Student	-	-	4 (2.2)	1.1- 6	-	-	46 (45.5)	35.4-54.3
Smoking								
Yes	-	-	2 (1.1)	0.5-4.6	-	-	5 (5)	2.7-12.1
No	-	-	182 (98.9)	95.4-99.5	-	-	96 (95)	87.9-97.3
Alcohol								
Yes	-	-	22 (12)	8.5-17.6	-	-	25 (24.8)	17.9-34.4
No	-	-	162 (88)	82.4-91.8	-	-	76 (75.2	65.6-82.1

Table 2. Baseline levels of CD4 count among the HIV positive respondents.

Respondent group		Number	CD4+ cell counts (Mean±SEM)		
			Baseline	3 Months	6 Months
HIV positive	All	184	333±19.7	501.6±25.4	497.1±19.7
	CD4+ <200 cells/mm^3	22	119±15.1	261.4±54.7	279.4±59.6
	CD4+200-499 cells/mm^3	86	376.5±19.9	402.8±38.7	363.8±9.2
	CD4+ ≥500 cells/ mm^3	76	723.8±32.2	666.7±49.1	720.8±27.5
	ARV treated	152	502.7±23.5	548±29	538±22
	ARV naive	32	562.7±68.6	279±19	301±24

333.0 ± 19.7 cells / mm^3. Follow up data on the HIV positive respondents indicated that the CD4+ levels at three and six months were elevated to 501.6±25.4 and 497 ± 19.7 cells / mm^3, respectively. The HIV positive respondents were categorized into three groups, according to WHO guidelines, and the CD4+ cell counts for each category determined. The details of the CD4+ baseline values are given in Table 2.

Differences in biochemistry parameters in HIV negative respondents.

HIV-negative male respondents showed significantly higher mean values than those of HIV negative female respondents in: alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin and creatinine. The mean values of these parameters were analyzed for male and for females separately in the HIV positive respondents. Details of the compared male and female biochemistry parameters are demonstrated in Table 3.

Changes in biochemistry parameters in HIV positive respondents over time

Significant increases in GGT mean values above the control upper limit were observed in HIV positive

Table 3. Differences in biochemistry mean values between male and female HIV negative respondents

Parameter	Respondent group						P-value
	HIV negative all (n = 101)		Male (n = 75)		Female (n = 26)		
	Mean (SEM)	95% CI	Mean (SEM)	95% CI	Mean (SEM)	95% CI	
ALT (u/L)	23.1 (1.43)	20.5-26.2	25.8 (1.66)	22.5-29.1	16.3 (2.31)	11.5 -21.0	0.002**
AST (u/L)	27.1 (0.96	25.2-29	28.5 (1.17)	26.2-30.8	23 (1.31)	20.3-25.6	0.010*
G-GT (u/L)	25.3 (0.95)	22.1-28.6	26.6 (1.77)	23.1-30.1	21.8 (3.88)	13.8-29.8	0.421
ALP (u/L)	103.4 (3.93)	95.6-111.2	106.6 (4.94)	96.7-116.4	94.4 (5.14)	83.6-105.1	0.175
T.Bil (µmoles/L)	6.7 (0.35)	6.0-7.4	7.4 (0.42)	6.6-8.3	4.6 (0.41)	3.8-5.5	<0.001**
D.Bil (µmoles/L)	3.2 (0.16)	2.8-3.5	3.4 (0.2)	3.0-3.8	2.5 (0.14)	2.2-2.7	<0.001**
T.P (g/L)	68.5 (0.68)	67.1-69.8	69.1 (0.75)	67.6-70.6	66.6 (1.41)	63.7-69.8	0.099
ALB (g/L)	47.6 (0.44)	46.8-48.5	48.1 (0.49)	47.1-49.1	46.3 (0.92)	44.4-48.2	0.075
CRT (µmoles/L)	89.8 (2.0)	85.8-93.8	95 (2.03)	91-99.1	74.7 (3.82)	66.7-82.7	0.002**
UR (mmoles/L)	3.4 (0.13)	3.1-3.7	3.5 (0.17)	3.2-3.8	3.1 (0.15)	2.8-3.5	0.21

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; G-GT, L-gamma-glutamyl transferase; ALP, alkaline phosphatase; T.BI, total bilirubin; D.BIL, direct bilirubin; TP, total protein; ALB, albumin; CRT, creatinine; UR, urea. *Significant differences between male and female mean values at P < 0.05 (two-tailed) using t-test; **Significant differences between male and female mean values at p < 0.01 (one-tailed) using t-test.

respondents at baseline stage in: CD4+ < 200 -, 200 – 499 - and CD4+ ≥ 500 cells /mm^3 groups. This parameter however, showed significant decrease from the baseline stage to the third and to the sixth months' stages of the study in CD4+≥ 500 cells /mm^3 group. In ALP significant decrease of the mean value below the control lower limit was observed at baseline stage in CD4+ 200 – 499 cells /mm^3 group; while significant increase was observed in CD4+ ≥ 500 cells /mm^3 group. The parameter showed significant decreases between: the baseline and the sixth month's samples in CD4+ 200 – 499 cells /mm^3 group and between the baseline mean value and the mean value of the sixth month's sample in CD4+≥ 500 cells /mm^3 group. When all the mean values of ALP in the CD4+ 200 – 499 cells/mm^3 group were compared, they were significantly different. Albumin showed significant decreases below the control lower limit in the baseline mean values in the CD4+ cell groups. Urea (UR) demonstrated significant decreases below the control lower limit in the baseline mean values in: CD4+ 200 – 499 - and CD4+≥ 500 cells /mm^3 groups. Details of these changes are shown in Table 4.

Changes in biochemistry parameters in HIV positive male respondents over time

Significant increase in ALT mean values above the control upper limit was only observed at the baseline stage in CD4+ 200 – 499 cells /mm^3 group. Within this CD4+ group the parameter showed significant increase between baseline and the third month's mean values, followed by a significant decrease in the sixth month's mean value. There was a significant difference among the mean values of the parameter in the group. In the CD4+ < 200 cells /mm^3 group, ALT showed a significant increase between the baseline mean value and the sixth month's mean value. The parameter increased significantly above the baseline mean value in the third month sample, then decreased significantly in the sixth month's sample. When compared, the means of this parameter were significantly different in the CD4+ ≥ 500 cells /mm^3 group. Aspartate aminotransferase mean value was significantly increased above the control upper limit in the baseline stage of CD4+ 200 – 499 cells /mm^3 group. It also increased significantly between the baseline and the third month samples. On comparison, all the means of the parameter in the CD4 group were significantly different. Significant decrease in AST mean value was observed between the baseline and the sixth month's mean values in CD4+ ≥ 500 cells /mm^3 group. Direct bilirubin (D. Bil) demonstrated significant decrease below the control lower limit at baseline stages of both CD4+ 200 – 499 - and CD4+≥ 500 cells /mm^3 groups. The means of parameter showed significant decrease from the baseline to the third month and then to the sixth month's values in CD4+ < 200 cells/mm^3 group. All the means of this parameter in the CD+4 group were significantly different when compared. Creatinine increased significantly above the control upper limit at baseline and third month stages in CD4+200 - 499 cells/mm^3 group but decreased significantly in the sixth month' s sample. When all the mean values of the parameter in CD4+200 - 499 cells/mm^3 group were compared, they were significantly different. The details of these changes are shown in Table 5.

Changes in biochemistry parameters in HIV positive female respondents over time

Significant increase in ALT mean values above the

Table 4. Changes in Biochemistry parameters in HIV positive respondents over time.

Parameter	Respondent group									
	HIV negative all (N = 101)	HIV – positive all (n = 184)								
		CD4+ <200 cells/mm^3 (n = 22)			CD4+ 200 – 499 cells/mm^3 (n = 86)			CD4+ ≥ 500 cells/mm3 (n = 76)		
		F_0	F_1	F_2	F_0	F_1	F_2	F_0	F_1	F_2
	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM
G-GT u/l	25.3± 0.9	37± 2.69**	36.3± 0.94	31.8± 2.0	59 ± 4.78**	67.2± 5.05	56.8± 4.65	62.5± 7.83**c	56.6± 5.65b	53.3± 6.80a
ALP u/l	103.4± 0.93	81.8± 9.28	85.2± 3.69	78.0± 4.61	95.9 ± 3.65**b	97.7± 4.21	82.2± 3.78a,d	110.5± 5.04**	102.9±3.99	89.9± 3.81a
T.P g/l	68.5± 0.68	66.3± 1.37**	67.5± 0.81c	57.3± 1.47a,d	64.5 ± 1.46b	69.5 ± 0.92c	63.1± 0.78a,d	65.5± 0.94b	67.5± 0.92c	60.6± 0.1a,d
ALB. g/l	47.6± 0.44	43.2± 1.22**	42.2± 0.70	40.3± 0.85	44 ± 0.53*	45.7± 0.50	43.7± 0.57	45.4± 0.56**	45.2± 0.44	42.4± 0.61
UR µ/l	3.4± 0.13	2.9± 0.34	3.2± 0.30	1.7± 1.17	2.9 ± 0.11**	3± 0.12	2.6± 0.10	3.1 ± 0.13**	2.8 ± 0.14	2.4± 0.15

F_0 = Baseline, F_1 = Follow up at 3 months; F_2 = Follow up at 6 months. *Significant difference in mean values at p<0.05 (two-tailed) between HIV negative respondent and HIV positive respondents at baseline using t-test; **Significant difference in mean values at p<0.01 (one-tailed) between HIV negative respondents and HIV positive respondents at baseline using t-test. a, b, c Significant differences (p< 0.05) in mean values between: F_0 and F_1; F_1 and F_2 within CD4 groups in the order of mean vales: a< b< C using t-test. [d]Significant difference (p< 0.01) within CD4 group using ANOVA for multiple comparisons.

Table 5. Changes in Biochemistry parameters in HIV positive male respondents over time

Parameter	Respondent group									
	HIV negative males (n = 75)	HIV positive males (n = 65)								
		CD4+ < 200 cells/mm^3 (n = 13)			CD4+ 200 – 499 cells/mm^3 (n = 43)			CD4+≥ 500 cells/mm^3 (n = 9)		
		F_0	F_1	F_2	F_0	F_1	F_2	F_0	F_1	F_2
	Mean±SEM	Mean± SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM
ALT u/l	25.8± 1.66	28.0± 1.96a	23.15± 2.2	31.67± 6.6b	31.49± 0.86*b	32.00± 2.72c	28.69± 3.2a,d	27.0± 4.84b	42.4± 7.5c	23.60± 3.74a,d
AST u/l	28.5± 10.17	28.0± 4.84	28.36± 4.98	22.6±1.78	38.21± 4.28*a	47.17± 5.1b,d	33.17± 7.88	29.90± 6.90b	39.2± 8.0	29.7± 5.80a,d
T.Bil µmoles/l	7.43± 1.66	4.2± 1.57c	2.88± 0.68a	3.41± 0.30b	4.09± 0.35**	5.10± 0.41	5.08± 0.39	5.12± 0.87 *	5.31± 0.38	4.55± 0.47
D. Bil µmoles/l	3.4 ± 0.20	2.48± 0.69	1.93± 0.42	0.84± 0.29	2.68± 0.34**c	1.82± 0.20b	1.47± 0.24a,d	1.82± 0.48*	2.49± 0.2	1.40± 0.41
CRT µmoles./l	95.0± 2.03	105.9±16.28	94.23± 7.21	80.7±10.36	95.67± 3.31a	127.95±18.7c	98.36± 4.93b,d	98.6± 5.53b	112± 11.2	78.5± 11.66a

F_0 = Baseline; F_1= Follow up after 3 months; F_2 = follow up after 6 months. * Significant difference between HIV negative mean value and HIV positive mean value at baseline at p < 0.05 (two-tailed) using t-test. **Significant difference between HIV negative mean value and HIV positive mean value at p < 0.01 (one-tailed) using t-test. a, b, c Significant difference (p <0.05) in mean values between F_0 & F_1 and F_1 & F_2 within CD4+ cell groups in the order of means a<b<c. d Significant difference (p < 0.05) in mean values within a CD4+ group.

control upper limit was observed in CD4+ ≥ 500 cells / mm^3 group at baseline stage. The parameter also increased significantly between the baseline and the sixth month's samples in the same group. There was a significant increase in AST mean values between the baseline and the third month's sample in CD4+ < 200 cells /mm^3 group with a significant difference among the mean values in the group. Aspartate

Table 6. Changes in biochemistry parameters in HIV positive female respondents over time

Parameter	Respondent group									
	HIV negative females (N = 26)	HIV positive females (n = 119)								
		CD4+ < 200 cells/mm^3 (n = 9)			CD4+ 200 – 499 cells/mm^3 (n = 43)			CD4+ ≥500 cells/mm^3 (n = 67)		
		F_0	F_1	F_2	F_0	F_1	F_2	F_0	F_1	F_2
	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM
ALT u/l	16.3± 2.16	19.0± 2.40	20.71± 1.79	19.20± 4.55	23.12± 2.53	24.53± 2.1	24.64± 2.12	25.90±1.28**^{a}	26.25± 2.26	26.87±3.0^b
AST u/l	23±1.29	27.22±1.063^a	36.56±13.24^b	20.13± 2.43^d	30.07± 3.29	33.86±1.93	23.23± 1.60	34.62± 3.14*^{b}	37.37± 4.45	25.40± 2.26^{a,d}
T.Bil µ moles/l	4.6 ± 0.41	3.50 ±1.04^b	3.41 ± 0.29^a	3.76± 0.50^{c,d}	3.17± 0.36*^{a}	4.42± 0.38^c	3.58± 0.23^{b,d}	3.07± 0.40**^{a}	3.65± 0.17^b	3.66± 0.23 ^{c,d}
D. Bil µ moles /	2.5± 0.12	2.61± 0.62^b	1.36 ± 0.44	1.36± 0.39 ^{a,d}	1.57± 0.23**	1.68± 0.23	1.03± 0.22	1.06± 0.20**^{b}	1.18± 0.15^c	1.03± 0.16^{a,d}
CRT µ moles./l	74.7±3.45	103.18± 16.43*^{b}	105.25± 22.87^c	76.11± 19.24 ^{a,d}	84.05± 3.1^b	89.07± 3.59^c	76.07± 3.35^a	80.98±18.59	90.06± 2.01^b	78.27± 2.34^{a,d}

F_0 = Baseline, F_1 = Follow up at 3 months, F_2 = Follow up at 6 months *Significant difference between HIV negative mean values and HIV positive at baseline at p<0.05 (two-tailed) using t-test. **Significant difference between HIV – negative mean values and HIV positive. Baseline mean values at p<0.01(one-tailed) using t-test. a, b, c Significant differences (p <0.05) in mean values between: F_0 and F_1; F_1 and F_2. within CD4 groups in the order of mean values: a< b< C. d Significant difference in mean values (p< 0.01) within CD4 group using ANOVA for multiple comparison.

aminotransferase demonstrated significant increase above the control upper limit in CD4+ ≥ 500 cells /mm^3 group. When all the mean values of this parameter in CD4+ ≥ 500 cells /mm^3 group were compared, they differed significantly. Total bilirubin showed significant decrease below the control lower limit cells / mm^3 at baseline stages of: CD4+ 200 – 499 - and CD4+ ≥ 500 cells /mm^3 groups. The mean values of this parameter in CD4+< 200 cells / mm^3 group decreased significantly between the third and the sixth months' samples. When the mean values of this parameter in the same group were compared, they differed significantly. Total Bilirubin demonstrated significant increases between the baseline and the third month's mean values in CD4 + ≥ 500 cells /mm^3 group. All the mean values of the parameter in the CD4+ group differed significantly when compared. Direct bilirubin mean values increased significantly above the control upper limit at the baselines stages of CD + 200 – 499 - and CD4+ ≥ 500 cells /mm^3 groups. The mean values of this parameter decreased significantly between the baseline and the sixth month's samples in CD4+ < 200 cells / mm^3 group. When all the mean values of the parameter in the CD4+ group were compared, they were significantly different. In CD4+ ≥ 500 cells/mm^3 group D. Bil showed significant increase between the baseline and the third month's mean values but significantly decreased between the third and the sixth months' mean values.

Creatinine mean values significantly increase above the controls upper limit in CD4+ < 200 cells /mm^3 group at the baseline stage. The values also increased between the baseline and the third month's samples but significantly decreased between the third and the sixth months' samples in the CD4+ group. When the mean values of the parameter in the CD4+ group were compared, they were significantly different. The mean values of CRT demonstrated significant increases between the baseline and the third month's samples and significant decreases between the third and the sixth months' samples in CD4+ 200 – 499 cells /mm^3 group. Similar changes of the mean values of CRT were observed in CD4+ ≥ 500 cells /mm^3 group (Table 6).

DISCUSSION

Among the HIV seronegative respondents, significantly higher ALT (p = 0.002), AST (p = 0.01) and CRT (p = 0.01) mean values in males than in females were confirmed (Koran et al., 2007). These gender-based variations have been previously attributed to the direct effect of sex hormones (Murphy, 2014).

The observed significantly higher T. Bil and D. Bil in males than in females has not been reported elsewhere. Among the HIV positive respondents, the levels of G-GT increased by up to about one

and a half times above referents upper limit in CD4+ < 200 cells/mm^3 group and by between two and about two and a half times above the limit in both CD4+ 200 – 499 - and ≥500 cells/mm^3 groups. The higher GGT levels observed in CD4+ 200 - 499 and in CD4+ ≥500 cells/mm^3 groups may be related to higher white blood cells count, red blood cells count, higher hematocrit and haemoglobin levels which may characterize these groups. These parameters have been associated with levels of G-GT in earlier reports (Ramana et al., 2012). Conversely, the decreases in ALP mean values below the control lower limit were most marked in CD4+ < 200 cells/mm^3 group. Decreased ALP levels have been reported in cardiac surgery and cardiopulmonary bypass, malnutrition, magnesium deficiency, hypothyroidism and severe anemia (Lum, 1995). Increases in GGT levels with decreases in ALP levels have been associated with cardiac related disorders (Jiang et al., 2013) rather than biliary disease (Lum and Gambino, 1972). Levels of HIV – associated anemia are reported to increase with the severity of the disease (Meidani et al., 2013). In this study CD4+ < 200 cells /mm^3 represent the severest stage of HIV. Subsequently high levels of anemia that could characterize the stage may be one cause of the marked decreases in ALP observed. This would be confirmed by determining hemoglobin levels.

Slight to moderately elevated levels of ALT and AST were observed in both male and female HIV positive respondents with no CD4+group based characteristic trends. This shows changes in these two enzymes are not affected by changes in CD4+ cells. Earlier reports have indicated that HIV disease progress does not alter the levels of these two liver enzymes (Dusingize et al., 2015). Increases in ALT and AST have previously been reported in myocardial infarction, acute liver cell damage, viral hepatitis and carbon tetrachloride poisoning (Dusingize et al., 2015; Netto et al., 2009). Levels of hypoalbuminemia decreased with increases in CD4+ cells suggesting that there may be altered albumin: globulin ratio; levels of globulins will be higher in CD4+ < 200 cells/mm^3 group. This consequently suggests that levels of hypergammaglobulinemia in HIV reported elsewhere (Audu et al., 2004; Patil and Raghuwanshi, 2009) is highest in this stage of the disease marking the severity of this disease. Determination of albumin: globulin ratios would confirm these suggestions. Hypoalbuminaemia in HIV infection has also been reported previously following use of certain antiretroviral agents (Ibeh et al., 2013). The observed decreases in both the total and direct bilirubin in HIV positive respondents is clinically insignificant; only hyperbilirubinemia is of significance in HIV infection and arises from jaundice, liver disease, hemolytic anemia and blockage of the bile duct (Wolf, 1999; VanWagner and Green, 2015). Increased levels of creatinine in HIV positive respondents observed did not demonstrate any trends in the CD4+ groups indicating that the serum levels of this parameter are not associated with HIV disease progress.

Establishment of gender – based reference ranges for T. Bil and D. Bil values are recommended. Assays of cardiac enzymes in monitoring the progress of HIV management are recommended. Determination of Albumin: globulin ratios in HIV monitoring is recommended Albumin is a carrier protein for bilirubin, hormones, metals, vitamins, and drugs (Merlot and Richardson, 2014; Naveen et al., 2016). So the impact of hypoalbuminemia on drug therapies and food supplements in the management of HIV-associated pathologies need to be determined. Similar study on ARV- treated and ARV- naïve patients separately is recommended.

Study limitations

The recruitment of study respondents was not randomized and this may have reduced the strength of making population inferences of the studied characteristics. The details of antiretroviral therapy regimens and HIV-coinfection and their therapies were not put into account in this research work.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

REFERENCES

Agbaji OO, Onu A, Agaba PE. Muazu MA, Falang KD, Idoko JA (2011). Predictors of impaired renal function among HIV infected patients commencing highly active antiretroviral therapy in Jos, Nigeria. Niger. Med. J. 52(3):182-185.

Amanzada A, Goralczyk AD, Reinhardt L, Moriconi F, Cameron S, Mihm S (2011). Erythropoietin rs1617640 G allele associates with an attenuated rise of serum erythropoietin and a marked decline of hemoglobin in hepatitis C patients undergoing antiviral therapy. BMC Infect. Dis. 14:503.

Audu RA, Akanmu AS, Mafe AG, Efienemokwu C, Musa AZ, Lemoha E, Odunaike MI, Funso-Adebayo EO, Meshack E, Idigbe EO (2004). Changes in Serum Proteins and Creatinine levels in HIV Infected Nigerians. Niger. J. Health Biomed. Sci. 3(2):69-72.

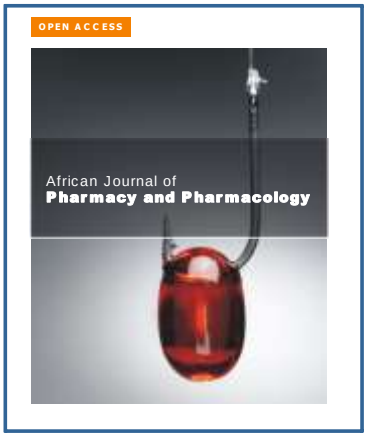
Beverborg GN, Verweij N, Klip T van der- Wa H, Voors A, van Veldhuisen D, Gansevoort N, Bakker S, Harst P, Meer P (2015). Erythropoietin in the General Population: Reference Ranges and Clinical, Biochemical and Genetic Correlates. PLoS One 10(4):e0125215.

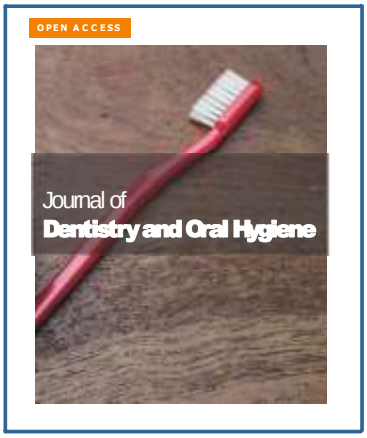
Clark JM, Brancati FL, Diehl AM (2003). The prevalence and etiology of elevated aminotransferase levels in the United States. Am. J. Gastroenterol. 98(5):960-967.

Dusingize JC, Donald R, Shi HQ, Mutimura E, Rudakemwa E, Ndacyayisenga V, Gakindi L, Mulvihill M, Sinayobye J, Musabeyezu E, Anastos K (2015). Association of Abnormal Liver Function Parameters with HIV Serostatus and CD4 Count in Antiretroviral-Naive Rwandan Women. AIDS Res. Hum. Retroviruses 31(7):723-730.

Ganz T, Nemeth E (2012). Hepcidin and iron homeostasis. Biochim. Biophys. Acta 1823(9):1434-1443.
Hunziker L, Recher M, Macpherson AJ (2003). Hypergammaglobulinemia and autoantibody induction mechanisms in viral infections. Nature Immunol. 4:343-349.
Ibeh B, Omodamiro O, Ibeh U, Habu J (2013). Biochemical and haematological changes in HIV subjects receiving winniecure antiretroviral drug in Nigeria. J. Biomed. Sci. 20(1):73.
Jiang S, Jiang D, Tao Y (2013). Role of gamma-glutamyltransferase in cardiovascular diseases. Exp. Clin. Cardiol. 18:53-56.
Koran K, Addae M, Ocran J, Adu-Amankwah S, Rogers WO, Nkrumah FK (2007). Population based reference intervals for common blood haematological and biochemical parameters in the Akuapem North district. Ghana Med. J. 41:160-166.
Limdi JK, Hyde GM (2003). Evaluation of abnormal liver function tests. Postgrad. Med. J. 79(932):307-312.
Lum G (1995). Significance of Low Serum Alkaline Phosphatase Activity in a Predominantly Adult Male Population Clinical. Chemistry 41(4):515-518.
Lum G, Gambino SR (1972). Serum gamma-glutamyl transpeptidase activity as an indicator of disease of liver, pancreas, or bone. Clin. Chem. 18(4):358-362.
Mata-Marín JA1, Gaytán-Martínez J, Grados-Chavarría BH, Fuentes-Allen JL, Arroyo-Anduiza CI, Alfaro-Mejía A (2009). Correlation between HIV viral load and aminotransferases as liver damage markers in HIV infected naive patients: A concordance cross-sectional study. Virol. J. 6:181.
Meidani M, Rezaei F, Maracy RM, Avijgan M, Tayeri K (2013). Prevalence, severity, and related factors of anemia in HIV/AIDS patients. J. Res. Med. Sci. 17(2):138-142.
Merlot AM, Richardson DR (2014). Unraveling the mysteries of serum albumin –more than just a serum protein. Front. Physiol. 5:299.
Murphy WG (2014). The sex difference in haemoglobin levels in adults –Mechanisms, causes, and consequences. Blood Rev. 28(2):41-47.
Naveen R, Akshata K, Pimple S, Chaudhari PA (2016). Review on albumin as drug carrier in treating different diseases and disorders. Pharm. Sin. 7(1):11-15.
Netto I, Borgaonkar K, Lobo R (2009). Aminotransferase profile in HIV positive patients. Indian J. Sex. Transm. Dis. 30(2):121.
Patil R, Kamble P, Raghuwanshi U (2013). Serum ALP and GGT Levels in HIV Positive patients. Int. J. Recent Trends Sci. Technol. 5(3):155-157.
Patil R, Raghuwanshi U (2009). Serum Protein, Albumin, Globulin Levels, and A/G Ratio in HIV Positive Patients. Biomed. Pharmacol. J. 2(2):321-325.
Poles MA, Lew EA, Dieterich DT (1997). Diagnosis and treatment of hepatic disease in patients with HIV. Gastroenterol. Clin. North Am. 26:291-321.
Rahman MM, Giti S, Islam MS, Rahman MM (2014). Haematological Changes in Peripheral Blood of HIV –Infected Persons with Correlation to CD4 Cell Count. J. Bangladesh Coll. Phys. Surg. 32:130-136.
Ramana KV, Rao R (2012). Abnormal levels of γ-glutamyl transpeptidase (GGTP), ALT, AST in human immunodeficiency virus-1 (HIV-1) infection. Biochem. Physiol. 1(101):2-4.
Scarpino M, Santoro M, Pellicano G (2015). HIV infection and kidney disease: literature review. Infect. Dis. Trop. Med. 1(4):E195.
VanWagner L, Green R (2015). Evaluating Elevated Bilirubin Levels in Asymptomatic Adults. J. Am. Med. Assoc. 313(5):516-517.
Wolf PL (1999). Biochemistry Diagnosis of liver disease. Indian J. Clin. Biochem. 14(1):59-90.

Related Journals:





www.academicjournals.org