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Research Article

Effects of hiv infection on cluster of differentiation 4 and erythropoietin values as predictive indicators in hiv infected patients receiving heart at g.h nsukka in enugu

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Abstract

Background: This study delves into the historical foundations and contemporary landscape of pediatric neurology, tracing the contributions of key figures and the emergence of scholarly inquiry into conditions such as cerebral palsy and muscular dystrophy.

Materials and Methods: Through bibliometric analysis of over 1000 Google Scholar Citation profiles from 174 developing countries, the study identifies academic leaders in clinical pediatric neurology based on their H-index. Notable clinicians from diverse regions with an H-index of 20 or higher are highlighted, shedding light on disparities in academic productivity and opportunities for collaboration and knowledge exchange. Results: The analysis revealed notable clinical pediatric neurologists from several developing countries, including Aamir Jalal Al-Mosawi from Iraq (H-index 23), Asindi A. Asindi from Nigeria (H-index 23), and José Luiz D. Gherpelli from Brazil (H-index 21). Additionally, individuals from Malaysia, United Arab Emirates, Egypt, Indonesia, and other countries demonstrated substantial academic impact, with H-indices ranging from 10 to 17.

Conclusion: This study highlights the contributions of academic leaders in clinical pediatric neurology from diverse backgrounds. By recognizing and supporting these individuals, we can advance research, improve clinical practice, and ultimately enhance outcomes for children with neurological disorders worldwide.

Keywords: pediatric neurology; evolution; pioneers; bibliometrics

Abbreviations

HIV-Human Immunodeficiency Virus, CD4- Cluster of Differentiation 4,ART-Antiretroviral Therapy, HAART- Highly Active Antiretroviral Therapy,OIs- Opportunistic Infections,EPO- Erythropoietin, Hb - Haemoglobin, RNA- Ribonucleic Acid, WHO- World health Organization, AIDS- Acquired immunodeficiency syndrome, NNRTI -Non- Nucloside Reverse Transcriptase Inhibitors, EDTA-Ethylene Diamine Tetraacetic Acid, ART-Antiretroviral therapy. HDP -Horseradish Peroxidase. ELISA-Enzyme Linked Immunosobent Assay, CART-Combination of antiretroviral therapy. ROS-Reactive Oxygen Species, TNF- Tissue Necrosis Factor.

Introduction

The human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS), which is marked by gradual and deadly immune system weakening as well as the appearance of opportunistic infections and tumors (Levy, 2009). Although immune system dysfunction and a decrease in the number and activity of CD4+ T cells are the hallmarks of HIV infection. It is also important to remember that HIV may also affect other cell types and organs (Borderi et al., 2009; Gandhi et al., 2012; Maggi et al., 2012; Kaul et al., 2006).Peripheral blood cytopenias, such as anemia,

neutropenia, and thrombocytopenia, arise in most patients with AIDS and some HIV-positive naive individuals during the early stages of disease progression, especially when high plasma levels of HIV RNA are detectable, in regards to progressive depletion of CD4+ T lymphocytes (Zon et al., 1987; Moses et al., 1998).

In otherwise asymptomatic HIV positive patients, isolated thrombocytopenia might be the initial clinical sign (Ratner, 1989). In the late stages of HIV infection, anemia and neutropenia are increasingly prevalent (Davis & Zauli, 1995). The symptoms of anemia in HIV-positive individuals are similar to those seen in HIV-negative patients, and anemia is generally diagnosed with a laboratory test based on a decrease in haemoglobin (Hb) value and erythrocyte count. By far the most abundant of the blood cells are erythrocytes. When the red blood cell count is between 4.2 and 5.2 million per milliliter of blood, the body functions best.Because red blood cells carry oxygen, if the quantity of red blood cells falls too low, the blood oxygen level will fall as well. When the kidney detects a reduction in red blood cell synthesis, it releases erythropoietin (EPO), a protein that increases erythropoiesis, or red blood cell formation.

The haemocytoblast splits into normocytoblast and one cell that begins to differentiate into a proerthroblast, a partially differentiated erythrocyte. As the proerythroblast differentiates, it will get smaller and lose its organelles in the process. The proerythroblast will enter the bloodstream from the bone marrow and transform into a reticulocyte, a premature erythrocyte without a nucleus but with a limited number of organelles. The reticulocyte will discharge the rest of the organelles, show haemoglobin on its surface, and eventually grow into a full red blood cell after two days in the blood.

According to several researches, HIV may interfere with the EPO-related feedback processes that govern red blood cell homeostasis. In many HIV patients, the presence of anemia is associated with a drop in serum EPO concentration that is independent of kidney injury, whereas decreasing Hb concentration stimulates EPO synthesis (Kreuzer et al., 1997). Furthermore, in vitro studies revealed that HIV-1 inhibited EPO production. Various processes have been proposed to explain the decrease in EPO levels.The cytokine-mediated production of reactive oxygen species, which in turn impairs the binding affinities of EPO inducing transcription factors, causes HIV-related upregulation of pro-inflammatory cytokines IL-1 and TNF- to directly down regulate EPO expression in vitro (Weiss, 2005).

Despite the fact that HIV has a significant influence on CD4 counts and EPO values, these measures (CD4 counts and EPO) are utilized as predictive indicators of HIV disease progression in HIV-infected patients receiving antiretroviral treatment (Mellors et al., 1997; Korenromp et al., 2009). The most extensively used medical treatment for HIV is antiretroviral medication, which lowers the virus's activity. After 12 months of HAART treatment, the use of zidovudine, lamivudine, and stavudine was linked to a significant increase in haemoglobin concentration, and the prevalence of anaemia reduced from 65.5 percent to 46 percent (Kibaru et al., 2015).In another study, by Huang et al. (2000), they discovered significant increases in mean Hb from 13.9 to 14.1 g/dl after 3 months of HAART treatment.

Notwithstanding HIV therapy and all efforts by global health organizations, many people living with the disease are still at risk because they lack access to testing, care, or medication, and there is no cure. According to research, steps must be taken to prevent life-threatening side effects such as HAART-related haematotoxicity (Nubila et al., 2012). Despite a dearth of evidence on HAART use in these places, the WHO has classified efavirenz, tenofovir with lamivudine, or emtricitabine plus nevirapine as the preferred first-line antiretroviral medicines in resource-constrained developing countries, based on availability, safety, and efficacy (WHO, 2016).

Once efavirenz is not an option, nevirapine is the NNRTI of choice. Patients on efavirenz-based HAART who received tenofovir-emtricitabine had a higher rate of HIV replication suppression than those who received zidovudine-lamivudine (Darin et al., 2010). In Nigeria, data on haematopoietic and inflammatory indicators is still scarce. The purpose of this study is to assess the effect of HIV infection on HIV/AIDS patients in Enugu North Senatorial Zone, Enugu State.

Materials and Methods

Study Design

The study employed a cross-sectional, prospective, hospital based clinical research on all consenting consecutive patients scheduled for ART treatment irrespective of age between the period of March 2020 to August 2020 at the General Hospital Nsukka that meet the eligibility criteria.

Area of the Study

The study was conducted at General Hospital Nsukka. This hospital is one of the seven general hospitals in Enugu state and also a comprehensive site for the testing and management of ART patients. Nsukka is a Local Government Area in Enugu State, South eastern Nigeria.

Subjects and Sample Size Determination

The sample size of 137 was determining using Cochran (1963) formula for determining sample size, after which 137 subjects were purposively selected.

Ethical clearance/ informed consent

An ethical clearance was obtained from the Research and Ethical Review Committee of the Ministry of Health in Enugu State. The letter's reference number was MH/MSD/REC20/128. Then, permission was taken from General Hospital Nsukka's higher management and the treatment regimen information about the patients was sourced from the electronic medical record of the hospital. The data was collected after obtaining written informed consent from both literate participants and the legal guardians of all illiterate participants. There was no financial compensation or provision for the study participants. To ensure confidentiality of data, the study participants were identified using codes, and unauthorized persons had no access to the collected data. Furthermore, all findings were utilized for the proper management of the patients. The study was conducted by collection of blood samples from the subjects with informed consents.

Questionnaire

A structured questionnaire was filled by the subjects/ participants in order to obtain demographic data, clinical history and treatment regimen whether on first or second line.

Inclusion and exclusion criteria

Subjects included were those of 15 to 60 years diagnosed as HIV seropositve and put on ART drugs. Exclusion subjects' categories were subjects above 60years and pregnant women with HIV seropositive were not included.

Blood specimen collection

A 10ml sterile disposable syringe was used to collect venous blood from each patient. This was divided into 5ml plain sample containers and 5ml ethylene-diamine-tetraacetic acid (EDTA) containers that were labeled with the subject's identification number, age, and gender. The blood sample was spun at 3000rpm for 5 minutes in the simple containers. Using a dry clean Pasteur pipette, the serum was separated from the red cells and pipetted into a dry clean simple specimen container. After then, the serum was kept at -200°C.

CD4 count Principle/Procedure

The CD4 count was performed using CY –Flow counters, which identify CD4 cells using a fluorometric approach (Westerman et al 1994). The process for counting and identifying CD4 + T-lymphocytes is described in this application note (subset of whole blood cells). The CD4 simple count kit uses fluorescent-labeled antibodies directed against the human cell surface antigen CD4 to identify cells in whole blood samples.

Erythropoietin principle/procedure

The erytropoietin immunoassay is a two-site enzyme linked immunosorbent test (ELISA) that measures Epo's physiologically active165 amino acid chain. It employs two mouse monoclonal antibodies to human Epo that are specific for well-defined Epo molecular regions. For detection, one mouse monoclonal antibody to human Epo has been biotinylated, while the other has been tagged with horseradish peroxidase (HRP).

Statistical Analysis: The results obtained in this study were analyzed statistically. These were expressed where appropriate as mean± standard deviation. T-test was used in testing hypotheses at 5 % level of significance

Results

Effect of HAART on CD4 counts of HIV patients

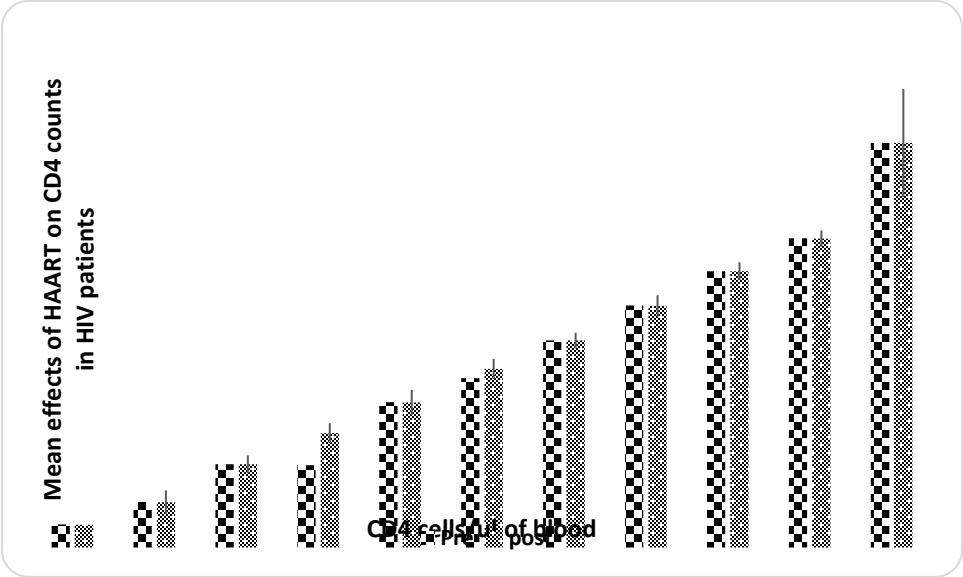
Table 1 shows the outcomes of CD4 counts in HIV patients with various CD4 ranges. The mean and standard error of CD4 counts of HIV patients before (pre) and after (post) HAART administrations are shown in Table 1. The grand mean CD4 counts before and post HAART administration were 632.37 ± 29.24 and 646.59 ± 28.95, respectively, as shown in the table. The difference in CD4 counts between pre and post, that is, before and after HAART was given to HIV patients, demonstrated that HAART enhanced CD4 levels.

The increase in CD4 counts in patients was statistically significant (P <0.05). This conclusion is comparable to that of Erb et al. (2000), who found that HIV-infected individuals who received a combination of RTI combination treatment and HAART had higher CD4 cell counts. A CD4 cell count rise of at least 50% of the baseline value was seen in almost 60% of the subjects treated with HAART (Erb et al., 2000). Mata et al. (2018) reported a similar conclusion, stating that commencing ART in HIV infected individuals raised CD4 from 96 cells/µL in 2003–05 to 173 cells/µL in 2010–13.

CD4cells/µl	CD4 Counts	
	Pre	Post
0-100	72.01 ±0.00	71.00± 0.00
101-200	140.77 ±0.38	140.00± 36.59
201-300	258.04 ± 0.01	257.43± 27.84
301-400	254.19 ± 0.03	353.46±31.05
401-500	449.34± 0.08	448.68± 39.16
501-600	523.35± 0.04	552.83± 30.68
601-700	641.04± 0.02	640.20± 24.17
701-800	748.31± 0.06	747.85± 32.46
801-900	854.05± 0.03	854.82± 27.42
901-1000	956.05± 0.03	955.20± 25.20
>1000	1251.39± 0.05	1250.77± 167.71
Grand Mean	632.37±342.30	646.59±338.89
t-test$_{0.05}$	* 0.03	

Table 1: Effect of HAART on CD4 counts in HIV patients.

Where; CD4=. P Value=Probability value, **=Significant at 0.05 level



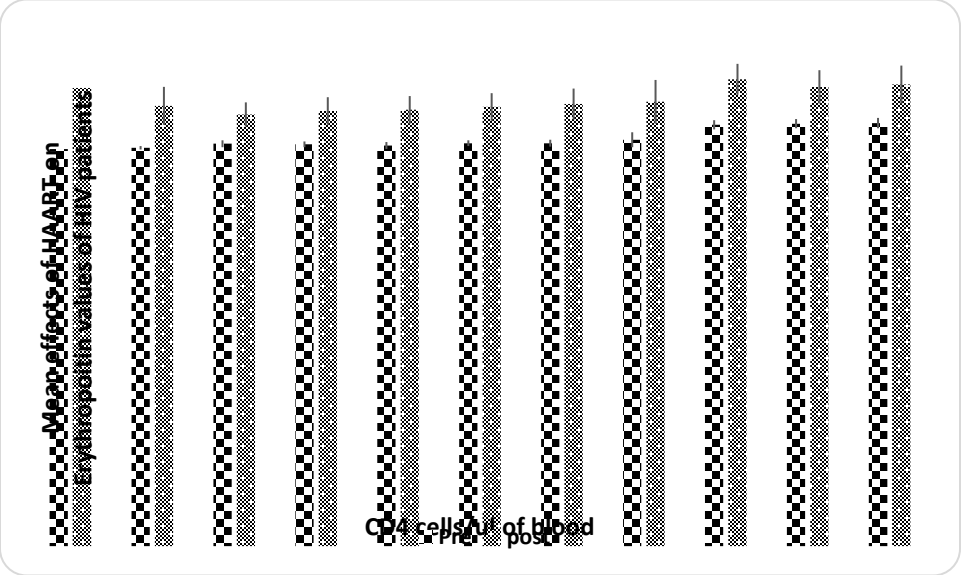
Effect of HIV infection on the erythropoietin of HIV infected patients

Table 2 shows the effects of HIV infection on EPO which is a haematopoietic cytokines in HIV infected individuals with various CD4 counts. The mean and standard error of erythropoietin (EPO) levels in HIV patients are shown in Table 2. The grand mean for the first (before) and subsequent (after) EPO levels of HIV patients was 7.10±0.01 and 7.74±0.03, respectively, as shown in the Table. The change in HIV patients' EPO levels between the two periods was significant (P <0.05). The difference in EPO levels indicated that HIV infection had the ability to decrease EPO synthesis in the body. In their investigation, Wang et al. (1993) discovered that HIV-1 appeared to suppress the synthesis of EPO and some, but not all, other cellular proteins, corroborating this conclusion. These findings imply that decreased EPO production may be a direct outcome of HIV-1 infection, potentially leading to anemia in AIDS patients.

CD4 cells/µl of blood	EPO mg/dl	
	Pre	Post
0-100	6.91 ±0.00	7.97± 0.00
101-200	6.93 ±0.03	7.66± 0.33
201-300	7.00 ± 0.06	7.51± 0.21
301-400	6.99 ± 0.05	7.57±0.24
401-500	6.97± 0.06	7.59± 0.24
501-600	7.01± 0.05	7.64± 0.24
601-700	7.01± 0.06	7.69± 0.27
701-800	7.07± 0.13	7.73± 0.38
801-900	7.33± 0.08	8.12± 0.27
901-1000	7.35± 0.08	7.99± 0.29
> 1000	7.36± 0.09	8.03± 0.33
Grand Mean	7.10±0.17	7.74±0.33
t-test$_{0.05}$	**0.00	

Table 2: Effect of HAART on EPO in HIV patients.

Where; CD4=, P Value=Probability value, **=Significant at 0.05 level, Erythropoietin values (mg/dl)



The behaviour of CD4 counts and haematopoietic cytokines of HIV infected patients after the administration of HAART

Table 3 shows the changes in CD4 counts and haematopoietic cytokines in HIV-infected individuals after treatment with HAART. The connection between CD4 counts and Erythropoietin levels following HAART treatment is seen in Table 3. There was a positive association between CD4 counts and Erythropoietin levels, as shown in the table, with r (136) = 0.63, p = 0.00.

Parameters	1	2
CD4 counts of HIV patients After HAART Administrati	-	
Erythropoietin values of HIV patients After HAART Administrati	**0.63**	-

Table 3: Correlation between CD4 counts and Erythropoietin values after the administration of HAART on HIV patients.

Correlation is significant at the 0.01 level (2-tailed), N = 137)

Discussion

HIV infection causes immune system weakening as well as decrease in cluster of differentiation 4 T cells and high plasma levels of HIV RNA. From the study, the CD4 T lymphocytes had an increase in the value when the patients were subjected to HAART, that was statistically significant (P<0.05). This agreed with the work of Erb er all 2000 that HIV- inflected individual who received CART had higher CD4 values which showed improved immune system.

When the value of the CD4+T cells go up there will be decrease in plasma levels of HIV RNA with the administration of HAART on preferred first - line anti retroviral medicines. The result from the EPO values showed that with the HAART , there was increase in the value. The grand mean for the EPO level pre and post was 7.10+-0.01and 7.74+-0.03mg/DL respectively, and showed statistically significant (P<0.05).The work of Wang et al 1993 discovered that, that appeared to suppress the synthesis of EPO. The in-vitro studies by Kreuzer et al 1997 showed that HIV-1 inhibits EPO production. The decrease in the EPO production is mediated by cytokine production of ROS and TNF. The study within six months showed an increase in CD4 , increase in EPO and HB as shown with the work of Huang et all 2000 that discovered significant increase in mean HB from 13.9g/DL to 14.1g/DL after 3months.

Conclusion

There is an increase in CD4 counts in patients in the study and is comparable to the work of Erb et al 2000, who found that HIV infected individuals who received a combination of antiretroviral therapy(CART) had higher CD4 counts. The change in HIV patient's EPO levels indicated that HIV infection had the ability to decrease EPO synthesis in the body. The work of Wang wt all 1993 discovered that HIV-1 appeared to suppress the synthesis of EPO and some, but not all. There was a positive association between CD4 counts and EPO level as r(136)= 0.63, P=0.00. The correction is significant at the 0.01level (2 tailed), N=137.

Recommendations

1. Global Health organization should step up the use of erythropoietin in monitoring HIV patients and to monitor the effective use of HAART.

2. The cluster of differentiation (CD4) +Tcell monitoring as a hallmark of HIV infection should be implemented in all the facilities in Nigeria.

Limitations:

1. The cost of materials

2. Money and time spent in data analyses.

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