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ORIGINAL RESEARCH

# CD4 Count and Anti Retroviral Therapy for HIV Positive Patients With Cancer in Nigeria -A Pilot Study

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**Abstract**

**Background:** Highly Active Anti Retroviral Treatment (HAART) improves the outcome of HIV positive patients treated for cancer. In our center HAART is only commenced in HIV positive patients with malignancy if the CD4 T lymphocyte count is less than 200 cells/ul. Presently, the outcome of treatment in these patients is poor.

**Objective:** To evaluate the influence of CD4 T- cell count and HAART on treatment outcome of HIV positive patients with cancer managed at the oncology service of The University College Hospital, Ibadan- South West Nigeria.

**Patients and methods:** Twenty two adult HIV positive patients with malignancies who presented for treatment at our hospital from 2007 to 2009 were closely monitored by the investigators. Relevant clinical data collected included age, sex, HIV status, type of malignancy, CD4 counts, history of ART, ECOG performance status, prescribed oncology treatment with regularity of treatment and to follow up conditions.

**Results:** Twenty two patients aged between 26 and 67 years were evaluated. The performance status of all patients was at least ECOG 2. Three ART naive patients with initial CD4 counts 450 cells/ul and above were able to complete oncology treatment without HAART with good malignant disease control. Five other patients on HAART before the diagnosis of malignancy with CD4 counts 350 cells/ul and above were also able to complete their treatments on schedule with good outcome. Eight HAART naive patients with initial CD4 counts less than 370 cells/ul had inconsistent treatments with poor outcome.

**Conclusion:** Based on these observations, we propose that HAART should be commenced on all HIV positive patients diagnosed with malignancy with an initial CD4 count less than 450 cells/ul in our environment. Further studies in low resource settings with appropriate sample sizes are however needed to validate these findings.

**Keywords:** CD4 count, cancer, HAART

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## Introduction

The prevalence of HIV infection is high in sub Sahara Africa and mortality from associated AIDS is quite high. The introduction of Highly Active Anti Retroviral Therapy (HAART) since 1996 has improved survival and quality of life with this disease especially in the developed countries due to reduction in opportunistic infections.[1] This improvement is also noticed in Sub Sahara Africa though access to ART is still a problem to most patients. The estimated coverage of ART in sub Sahara Africa is about 44%.[2] As HIV infected persons are living longer, non AIDS defining malignancies are becoming increasingly diagnosed.[3]

The mortality from cancer in underdeveloped countries is high and most of the patients present at advanced stage. There are also inadequate and unevenly spread of facilities for early diagnosis and effective treatment. Most patients are poor and cannot afford adequate treatment. The occurrence of cancer in HIV sero positive patient is therefore a challenging condition in a low resource setting. High morbidity and mortality of HIV positive patients diagnosed with cancer are consequently observed at our center. Highly Active Anti Retroviral Treatment (HAART) improves the outcome of HIV positive patients treated for cancer. it improves CD4 count level thus making it possible for cancer patients to receive chemotherapy and radiotherapy which are important modes of cancer treatment. These treatment modalities can also reduce the CD4 T- lymphocytes count hence the need to ensure their adequacy while on treatment.[4] At our center, HAART is only commenced in HIV positive patients with malignancy if the CD4 T lymphocyte count is less than 200 cells/ul. This is based on earlier WHO/CDC recommendation for ordinary HIV positive patients. Chemotherapy is usually commenced if the CD4 count is at least 200 cells/ul while Radiotherapy can be started in patients who are clinically fit despite CD4 count level.

## Objective

To evaluate the influence of CD4 T- cell count and HAART on cancer treatment compliance and outcome of HIV positive patients with cancer managed at the oncology service of The University College Hospital, Ibadan- South West Nigeria.

## Patients and Methods

Twenty two adult HIV positive patients with malignancies who presented for oncology treatments at the hospital from 2007 to 2009 were closely monitored by the investigators. Relevant clinical data collected included age, sex, HIV status, type of malignancy, CD4 counts, history of Anti Retroviral Treatment (ART), ECOG performance status, prescribed oncology treatment (chemotherapy/radiotherapy), consistency with oncology treatment and follow up conditions. Patients excluded from the study were those with ECOG performance status less than 2, those with no histological confirmation of malignancy, those with indeterminate HIV status and those who required radiotherapy alone. Viral load assay and specification of HIV 1 and 11 serotypes were not consistent in the patients. Radiotherapy was commenced as indicated in all the patients irrespective of CD4 count level. Chemotherapy was given if CD4 count was at least 200 cells/ul. ART naive patients with initial CD4 count less than 200 cells/ul were referred to HIV clinic for commencement of HAART. CD4 count was repeated monthly during oncology treatment and thereafter three monthly. Chemotherapy was suspended anytime the CD4 count value fell below 200 cells/ul.

### The procedure for the CD4 count assay was as follows

Blood samples were collected from the patients into EDTA bottles. Flow cytometry method was used to analyze the samples using CyFlow SL.3 brand of cytometer which uses green solid state laser with an excitation light source of 532 nm. It is connected to a computer system with flowmax software used in calculating the results. Partec test kit (from Partec GmbH of Germany) was used in preparing the samples. This test kit contains mouse monoclonal antibody (mAb) isotype IgG1 clone MEM-241 (this recognizes the human CD4 antigen) and no lyse buffer. A micropipette is used to withdraw 20 ul of EDTA anti coagulated whole blood sample into Rohren test tube to which 20 ul of CD4 mAb is added and mixed gently. The mixture is incubated in a dark cupboard at room temperature for 15 minutes. It is then removed and 800 ul of no lyse buffer is added and the mixture is shaken gently. The sample is then analyzed on the flow cytometer with the help of the computer system

which displays the results as CD4+ T- cell per ul of whole blood.

## Results

A total of 22 patients aged between 26 and 67 years were evaluated. Nine patients had cancer of the uterine cervix, 4 had non Hodgkin's lymphoma (NHL), 3 had nasopharygeal carcinoma, 3 had Kaposis' sarcoma while the remaining three had squamous cell carcinoma of the right jaw, right eye and breast cancer respectively. The performance status of 7 patients was ECOG 3 while 15 had ECOG 2. The characteristics and treatment outcome of the patients are presented in Table 1. From the table, three patients with cancer of the cervix had initial CD4 counts of 450, 460 and 500 cells/ul respectively. They were able to complete radiotherapy and chemotherapy as prescribed and were not commenced on HAART. Five other patients made up of three with cancer of the cervix, one with non Hodgkins lymphoma (NHL) and one with cancer of the breast were already on HAART before the diagnosis of malignancy. Their initial CD4 counts were from 350 to 370 cells/ul. They continued with HAART and were able to complete their treatments on schedule. These five patients were alive and well six months after treatment. Eight ART naive patients had initial CD4 counts between 250 and 320 cells/ul. All of them had values below 200 after one month of treatment. They were recommended to start HAART. Chemotherapy was suspended except radiotherapy until the CD4 count was at least 200. Two out of these patients died without completing their treatment while six are alive but with recurrent or persistent diseases and are on palliative care. One patient with squamous cell carcinoma of the right eye was on HAART. Her initial CD4 count was 420 cells/ul. She completed radiotherapy. Her CD4 count dropped to 120 cells/ul after the third course of chemotherapy. Further chemotherapy was suspended. Poor nutrition with non adherence to HAART were assessed to be contributory to the low CD4 count. She is alive with persistent disease. One patient with NHL had initial CD4 count of 150 cells/ul. This increased to 170 after one month of HAART but died before chemotherapy could be commenced. One

**Table 1.** Characteristics and outcome of HIV positive patients treated for malignancies (N = 22).

| Serial no. | Diagnosis | Initial CD4 | Previous HAART | Trt compliance | Outcome |
|---|---|---|---|---|---|
| 1 | cervix | 500 | No | Regular | Alive & well |
| 2 | cervix | 560 | No | Regular | Alive & well |
| 3 | cervix | 450 | No | Regular | Alive & well |
| 4 | cervix | 370 | Yes | Regular | Alive & well |
| 5 | cervix | 360 | Yes | Regular | Alive & well |
| 6 | cervix | 350 | Yes | Regular | Alive & well |
| 7 | cervix | 300 | No | Irregular | Alive + disease |
| 8 | cervix + TB | 260 | Yes | Irregular | Dead |
| 9 | cervix | 360 | No | Irregular | Dead |
| 10 | breast | 360 | Yes | Regular | Alive & well |
| 11 | nasopharynx | 350 | No | Irregular | Alive + disease |
| 12 | nasopharynx | 270 | No | Irregular | Dead |
| 13 | nasopharynx | 250 | No | Irregular | Dead |
| 14 | NHL | 350 | Yes | Regular | Alive & well |
| 15 | NHL | 250 | No | Irregular | Alive + disease |
| 16 | NHL | 250 | No | Irregular | Alive + disease |
| 17 | NHL | 150 | No | Irregular | Dead |
| 18 | SC Rt jaw | 280 | No | Irregular | Alive + disease |
| 19 | SC Rt eye | 420 | Yes | Irregular | Alive + disease |
| 20 | KS | 180 | No | Irregular | Alive + disease |
| 21 | KS | 80 | No | Irregular | Dead |
| 22 | KS | 46 | No | Irregular | Dead |

**Abbreviations:** NHL, non Hodgkins' lymphoma; KS, Kaposis' sarcoma; SC, squamous cell; Trt, treatment.

patient with Kaposis' sarcoma had initial CD4 count of 180 cells/ul. He was commenced on radiotherapy and HAART. The CD4 count dropped to 80 cells/ul in one month. He is alive but with persistent disease. Two other ART naïve patients with Kaposis' sarcoma had initial CD4 cells counts of 46 and 80 cells/ul respectively. They were given palliative radiotherapy and commenced on HAART. They died within three months of presentation. One cervical cancer patient who was on HAART with initial CD4 count of 260 cells/ul was also diagnosed with pulmonary tuberculosis and was on anti tuberculosis medications. She had palliative radiotherapy but could not receive the recommended chemotherapy She died within 4 months of presentation.

## Discussion

HIV infected patients are at increased risk of developing cancer. Apart from AIDS defining cancers like Kaposis' sarcoma (KS), Non Hodgkins lymphoma (NHL) and cervical cancer, non AIDS defining cancers are known to occur in excess in HIV sero positive patients. Such cancers include Hodgkins' lymphoma, anal cancer, multiple myeloma, leukemia, cancers of the lungs, lips, oral cavity, stomach, liver pancreas, larynx, vulva, vagina, kidney and childhood sarcoma.[5–7]

CD4 T- cell count serves as the major clinical indicator of immunocompetence in patients with HIV infection and hence usually the most important consideration in decision to initiate ART.[8] The use of HAART enables these patients to be treated as their immunocompetent counterparts with improved outcome.[9] The benefits of HAART include decreased development of HIV associated malignancies, higher CD4 count levels, improved tolerance of full dose of chemotherapy, improved response rates, duration of response and survival during treatment of malignancy.[10]

The WHO and USA Department of Health and Human Services (DHHS) have updated their recommendations on the commencement of ART in HIV positive patients to include those with CD4 count of 350 cells/ul or less in addition to the mandatory treatment of those with CD4 count less than 200 cells/ul which is still being used as the level for the commencement of ART in many places including our center. According to these guidelines, data from an ART cohort collaboration which included 61798 patients-years of follow up showed that at 3–5 years after starting ART, the risk of AIDS/death was significantly less in those who started therapy with CD4 T- cell count between 200 and 350 compared with those who initiated ART at a CD4 threshold of 200 cells/ul. Also the risk of opportunistic diseases and non AIDS events like hepatic failure, renal and cardiovascular diseases with non AIDS malignancies were higher in patients whose ART was deferred till CD4 count dropped to $<250$ cells/ul than in those who commenced treatment with CD4 count $>350$ cells/ul. There is also a recommendation that patients scenarios and co morbidities should be taken into consideration in starting ART in CD4 count $>350$ cells/ul.[11,12] The recent WHO recommendation to commence antiretroviral therapy when CD4 count is less than or equal to 350 cells/ul is for all HIV positive patients either symptomatic or not. In that same document under key recommendations on when to start treatment, ART should be commenced on all HIV positive patients with WHO stages 3 and 4 diseases irrespective of CD4 count. The WHO stage 4 disease includes lymphoma and cervical cancer which are malignant diseases.[13] This implies that patients with confirmed diagnosis of above conditions should be commenced on ART as soon as the diagnosis is made whether CD4 count is above 350 cells/ul or less. The panel placed high value on avoiding death, disease progression and HIV transmission over and above cost and feasibility in making these recommendations according to the report. This study though has small number of patients, is able to show that this group of patients needs separate approach to treatment as in other HIV associated situations like tuberculosis and infancy instead of approaching their treatment as ordinary HIV positive patients. This brings out the need for well planned studies in low resource settings to guide in developing management guideline that will help in improving the outcome of their treatment. Such studies might need to consider such factors like viral load, treatment failure and viral replication in suppressing improvements in CD4 cells count in HIV positive patients diagnosed with cancer.

In the developed countries, starting ART at CD4 count of 350 cells/ul or higher has been shown to be associated with significant reduction in the risk of death.[14,15]

This study shows that in our environment, waiting to commence HAART in HIV positive patients on oncology treatment when CD4 count is <200 cells/ul resulted in poor outcome. Patients with CD4 counts between 200 and 350 were not regular in their treatments due to drop in their CD4 counts below 200 resulting in poor outcome.

Chemotherapy has been successfully given to patients with CD4 cell counts less than 200 cells/ul mostly in developed countries. Such patients usually have the benefit of having haemopoetic agents like Granulocyte Colony Stimulating Factor (G-CSF) and erythropoietin. Autologous stem cell transplantation is recommended in cases of refractory or relapsed HIV associated lymphoma.[16] These agents are expensive in our center and hardly affordable by these patients most of whom are poor. Facilities for some of these interventions including those for early diagnosis and treatment of opportunistic infections are poor. Prophylaxis against pneumocystis pneumonia and mycobacterium avium are recommended in patients with CD4 cell counts less than 200 and 50 cells/iu respectively by the USA Department of Health and Human Services. The five patients with CD4 counts of 370 cells/ul who were already on HAART were able to complete their treatments on schedule confirming the benefit of HAART while on treatment. There is a report of a series of HIV positive patients with anal carcinoma where HAART was given to all patients even with CD4 count of 500 and above. They all received standard oncology treatments and had comparable results with HIV negative patients.[17] This shows that HAART can be commenced on those patients with higher CD4 count levels to ensure completion of oncology treatment in order to have comparable outcome with their HIV seronegative counterparts. There are concerns that ART are started too late in HIV positive patients in undeveloped countries when many patients are already immunocompromised hence an increase in the point of intervention to 400 or 450 cells/ul has been advocated.[18] The incidence of mortality has been shown to be higher in those who started ART with CD4 count less than 350 cells/ul.[19] The situation is thus very critical in HIV positive patients diagnosed with cancer because the malignancy itself and the modes of treatment which include surgery, chemotherapy and radiotherapy can all potentiate immunosuppression.[20] Most patients in low income countries do not have optimal nutritional status thereby worsening their immune states when challenged with above factors in addition to HIV infection. The earlier commencement of HAART in cancer patients with HIV infection may increase the number of patients requiring HAART but this increase is in a small cohort of patients. This will enable them to be treated as their sero positive counterparts with close monitoring of their CD4 counts. Compliance with anti retroviral medications should also be monitored in these patients as this is an important determinant of benefit with HAART.[21]

## Conclusion

Based on these observations, our assessment is that malignancy is an important co morbidity in HIV positive patients in low resource countries necessitating the early commencement of HAART. We therefore recommend that HAART should be commenced on all HIV positive patients diagnosed with malignancy with an initial CD4 count below 450 cells/ul in our environment to enable them complete their oncology treatments on schedule and CD4 count should be monitored in all such patients monthly until completion of oncology treatment. Further studies in low resource settings with appropriate sample size are however needed to validate these findings.

## Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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