CD4 + CELL RESPONSE TO ANTI-RETROVIRAL THERAPY (ARTs) IN ROUTINE CLINICAL CARE OVER ONE YEAR PERIOD IN A COHORT OF HAART NAIVE, HIV POSITIVE KENYAN PATIENTS

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ABSTRACT

Background: Untreated HIV/AIDS leads to severe immune depletion with opportunistic infections and other co-morbidities. Highly active anti-retroviral therapy (HAART) enhances immunity by sustained HIV- viral suppression, increase in CD4+ cell count and immune restoration. HAART reduces risk of neutropaenia, anaemia and accompanied decrease in incidence of opportunistic infections. Objectives: To study the CD4+ cell response in patients with severe HIV/AIDS disease over one year period while on HAART.

Design: Observational, descriptive, longitudinal study.

Setting: Kisumu District Hospital (Medical outpatient clinic, medical and surgical wards), Nairobi Rheumatology clinic and The Mater Hospital between July 2001 and March 2007.

Subjects: Four hundred and sixty three consenting patients were screened for the study.

Intervention: The 103 patients included received HAART within one to four weeks and appropriate treatment for the opportunistic infections and other co-morbidities. Various HAART combinations including combivir/efavirenz, stavudine/lamivudine/nevirapine and triomune 30/40 (fixed dose combination of stavudine, nevirapine and lamivudine) were used. Some delayed HAART because of the co-morbidities which had to be managed first (severe anaemia, hepatitis and meningitis).

Main outcome measures: CD4+ cell increase, new clinical events.

Results: Four hundred and sixty three patients were screened. One hundred and three patients (55 males and 48 females) were included and 360 (201 males and 159 females) patients were excluded. Mean age was 37.9 ± 9.0 years range of (15-70). The mean CD4+ cell counts over the study period were 141.7 ± 176.5 (1-1022), 192.4 ± 198.5 (3-1275), 221.2 ± 178.0 (3-1300), 247.2 ± 197.7 (1-1401) and 268.6 ± 189.9 (1-1390) cells/µl at 0, 3, 6, 9 and 12 months respectively. Nine patients had higher CD4+ cell counts > 350 cells/µl (433-1022) at baseline and higher HIV-viral RNA range between 51,830-1million copies/µl. The patients had multiple co-morbidities, namely, had tuberculosis, sepsis, cryptococcus meningitis, herpes zoster virus, four had non- Hodgkin's lymphoma, oral candidiasis, hepatitis B virus, pneumocytis jiroveci pneumonia and HIV with renal dysfunction. Seventy (68%) patients had ≥ 2 opportunistic infections. Mean AST, ALT and haemoglobin levels were 127.8 ± 79.8 IU/L, 157.2 ± 50.1 IU/L and 9.1 ± 4.3 g/dl respectively. No patient tested positive for anti-HCV antibodies.
Conclusion: The majority of patients had advanced HIV infection at baseline. There was a slow but steady increase in CD4+ cell count over one year. However only 30(29.1%) of patients achieved immune restoration. Seventy three (70.9%) of patients still had immune depletion with low CD4+ cell counts at one year of receiving HAART. Patients with low CD4+ cell counts at baseline had a steady increase of CD4+ cells over the first six months and this emphasises the need to initiate HAART early in public health policy strategy. Expedited HAART initiation should be done in patients with CD4+ cell counts < 350 cells/µl. Delayed HAART, at low CD4+ cell counts, is associated with poor immune recovery/restoration.

INTRODUCTION

Sub-Saharan Africa with fewer than 10% of the world’s total population accounts for 60% of HIV/AIDS cases worldwide. The key feature of untreated HIV/AIDS infection is the progressive depletion of CD4+ cell lymphocytes, increased HIV viral RNA and resultant severe immunosuppression. The advent of highly active anti-retroviral therapy (HAART) in 1996 profoundly changed positively the management of HIV/AIDS infections (1-5). Indeed, early initiation of HAART gives better clinical improvement (4, 5). HAART initiation leads to suppression of the HIV viral load to < 50 copies/µl, an increase in CD4+ cell count, dramatically decreases the incidence of opportunistic infections and leads to immune restoration (partial or complete), that is, reversal of HIV associated immunological alterations (3,7,8). This leads to a better quality of life of the patients (3-6).

The CD4+ cells are highly predictive of new AIDS events or death and enable the clinician to plan adequately for treatment (5, 6). Patients with advanced HIV disease, defined as those with CD4+ cell counts < 200 cells/µl, have a higher risk of progression of disease and opportunistic infections and other co-morbidities. Lately, WHO has recommended CD4+ cell count < 350 cells/µl as the new threshold to initiate HAART (7).

The study presents a cohort of HAART naïve patients with severe HIV disease and their subsequent CD4+ cell response to HAART over one year. It is noted that many studies do not include the very sick patients with HIV/AIDS in their protocols.

MATERIALS AND METHODS

A total of 463 (256 males and 207 females) consenting patients were screened for the study. Three hundred and sixty (201 males and 159 females) were excluded (referred to new Nyanza General Hospital other Mission Hospitals and health facilities offering free ART and care as they requested). One hundred and three patients (55 males and 48 females) were included. They were enrolled consecutively. They were able to be reviewed regularly for unscheduled medical attention and purchase ARTs (HAART was not universally available for all patients who were eligible). The patients were enrolled over a five year period (2001-2006) Table 2.

The ethics and standards committee at the Kisumu District Hospital approved the study. A signed, informed consent was obtained from each patient, for < 18 years old, signed by parent or guardian. All the patients were physically examined by one of the authors (MDs).

They included twenty four patients with known HIV positive sero-status from peripheral voluntary counselling and testing (VCT) centres and not on HAART. Some were newly diagnosed cases of HIV infection and diagnostic counselling and testing (DCT) was done and post-test adherence counselling done and sustained. From each patient, biodata were taken; seven millilitres of blood was drawn under aseptic condition from the cubital fossa and divided into two aliquots of four millilitres and three millilitres respectively. Three millilitres whole blood was used to analyse CD4+ cell count by the FACS flow cytometry machine. The other four millilitres of blood was used to do ELISA test for HIV diagnosis (for new patients). The ELISA method has a sensitivity and specificity of 99.9 and 98.9% respectively. The FACS flow cytometry machine has a sensitivity of 1-2000 cells/µl (FACS count machine from Baxton, Dickson).

CD4+ cell count was done at zero month and then every three months thereafter over one year period. With the increasing numbers of ART centres countrywide, majority of patients were transferred to these patient support centres (PSCS).

The included patients self purchased HAART from the established hospital chemists. HAART was defined as a combination of three Anti-Retroviral Drugs Vis-À-Vis Combivir (Lamivudine plus Zidovudine) + Efavirenz or fixed dose combination of Nevirapine, Stavudine, Lamivudine (as EMTRI 30/40) or Stavudine, Lamivudine, Nevirapine/ Efavirenz, which were the combinations readily accessible as first line therapies. Seventy three patients were promptly
initiated on HAART within one week.

Thirty patients delayed initiation of HAART due to the severe co-morbidities which they had and had to be managed first (nine, had severe anaemia, haemoglobin < 5g/dl, and received blood transfusion, 13 had elevated AST and ALT and nine of whom had hepatitis B virus infection and had to be given Livolin, a hepatotonic drug for liver regeneration and five had meningitis and three encephalitis and were in coma and had to be managed).

The CD4+ cell count threshold of 350 cells/μl was chosen because, it is the lower normal limit in the guidelines and clinically represents a point below which opportunistic infections occur more frequently and HAART initiation is recommended.

Interventions: All patients had HAART initiated promptly (7-29 days). HAART was defined as a combination of three anti-retroviral drugs (efavirenz + combivir, EMTRI 30/40, or Lamivudine+Videx+Efavirenz). The opportunistic infections and other co-morbidities were appropriately managed as in- or out- patients. The patients were subsequently followed up by the authors (MDs).

Data Analysis: Data were analysed in a cohort of patients with symptomatic HIV disease and majority had low CD4+ cell counts less than 350 cells/μl. The data were cleaned and analysed using the SPSS (version 11). Missing values (four patients) were imputed using the individuals previous or last CD4+ cell count value to give the nearest estimated CD4+ cell count at follow up. Individual as well as group CD4+ cell count means were estimated using the ANOVA procedures and emerging trends plotted as a line graph on an excel sheet to show the variations for each category over the one year follow up period. The patients’ CD4+ cell counts were stratified as, <200, 200-349, 350-499 and >500 cells/μl respectively.

RESULTS

Four hundred and sixty three patients (256 males and 207 females) were screened for the study. Three hundred and sixty patients were excluded and referred to other centres offering free HAART. (The study was conducted at a time when the government programme of free anti-retroviral drug access had not been fully rolled out).

The 103 patients included (55 males and 48 females) were enrolled and completed the study. The male: female ratio was 1.1:1. The mean age was 37.9 ± 9.0 years (range 15-70). Mean CD4+ cell count was 141.7 ± 176.5 cells/μl (1-1022).

Ninety four (91.3%) patients had CD4+ cell counts < 350 cells/μl (1-330). Nine (8.7%) patients had CD4+ cell counts > 350 cells/μl (433-1022 cells/μl) and had HIV-RNA load done to enable rational initiation of HAART. Their HIV-viral RNA range were between 51,830- > 1 million copies/μl. HAART was initiated in these patients with high CD4+ cell count to preserve immunity. One patient died at eight weeks (CD4+ cell count of 13 cells/μl) due to pneumocystis jiroveci pneumonia.

The CD4+ cell count means and ranges every three months, Table 2.

Figure 2 shows the graphical increase of the CD4+ cells over time.
Figure 1
Patient flow in the study

Table 1
Demographic and laboratory profile of the 103 study patients at initiation of HAART.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value(%, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M: F</td>
<td>55: 48 (1.1:1)</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>37.9 ± 9.0 (15-70)</td>
</tr>
<tr>
<td>Mean haemoglobin (g/dl)</td>
<td>9.1 ± 4.3 (8.9-15)</td>
</tr>
<tr>
<td><strong>CD4+ cell counts (cells/μl)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean CD4+ cell counts (350-1600 cells/μl)</td>
<td>141.7 ± 176.5 (1-1022)</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>4(4.0%) patients</td>
</tr>
<tr>
<td>350-499</td>
<td>5(4.8%) patients</td>
</tr>
<tr>
<td>200-349</td>
<td>11(10.6%) patients</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>83(80.6%) patients</td>
</tr>
<tr>
<td>*CDC clinical staging</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>3(3%)</td>
</tr>
<tr>
<td>B</td>
<td>10(9.7%)</td>
</tr>
<tr>
<td>C</td>
<td>90(87.3%)</td>
</tr>
<tr>
<td>AST(normal range - 5-40 IU/L)</td>
<td>127.8 ± 79.8</td>
</tr>
<tr>
<td>ALT(5-37 IU/L)</td>
<td>157.2 ± 50.1</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>20(19.4%) patients</td>
</tr>
<tr>
<td>Anti-Hepatitis C virus status</td>
<td>None</td>
</tr>
<tr>
<td>Creatinine ((normal range 60-120μmol/L)</td>
<td>100 ± 29.3 (59-176)</td>
</tr>
</tbody>
</table>

*CDC-Centres for Disease Control.
AST - Aspartate transaminase
ALT - Alanine transaminase
Figure 2
Age group gender based distribution of patients with HIV who were seen at initiation of ART at the medical outpatients clinics during routine clinic follow-up

Figure 3
Aligned dot plot showing a gradual increment in mean CD4+ counts for patients on treatment follow up over 12 months
Table 2
Mean CD4+ cell increase over 12 month period on HAART.

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Mean CD4+ (Range) cells/μl</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>141.7 ± 176.5 (1-1022)</td>
</tr>
<tr>
<td>3</td>
<td>192.4 ± 198.5 (3-1275)</td>
</tr>
<tr>
<td>6</td>
<td>221.2 ± 178.0 (3-1300)</td>
</tr>
<tr>
<td>9</td>
<td>247.2 ± 197.7 (1-1401)</td>
</tr>
<tr>
<td>12</td>
<td>268.6 ± 189.9 (1-1390)</td>
</tr>
</tbody>
</table>

Figure 4
Trends of CD4+ cells counts among HIV patients initiated on HAART and followed up for twelve months

Table 3
Co-morbidities/opportunistic infections/conditions in a cohort of HIV positive, HAART naïve patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (pulmonary, extra-pulmonary)</td>
<td>17</td>
</tr>
<tr>
<td>Sepsis*</td>
<td>6</td>
</tr>
<tr>
<td>Cryptococcus Meningitis</td>
<td>10</td>
</tr>
<tr>
<td>Herpes Zoster Virus</td>
<td>7</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Oral Candidiasis</td>
<td>31</td>
</tr>
<tr>
<td>Hepatitis B Virus</td>
<td>20</td>
</tr>
<tr>
<td>Pneumocystis Jiroveci pneumonia</td>
<td>7</td>
</tr>
<tr>
<td>(HIV associated nephropathy) HIVAN</td>
<td>2</td>
</tr>
<tr>
<td>Severe anaemia (haemoglobin &lt; 6.5 g/dl)</td>
<td>10</td>
</tr>
</tbody>
</table>

Sepsis (Pelvic Abscess 2, Ovarian abscess 1, Pyomyositis 2, Cervical region Abscess 1)
DISCUSSION

The study shows the CD4+ cell response in real clinical setting where patients have severe immunosuppression and > 1 co-morbidity. Use of HAART leads to suppression of HIV viral RNA, increase in CD4+ cell counts, decrease in opportunistic infections, a better quality of life and patients live longer (3-5). NASCOP recommends a CD4+ cell count of < 350 cells/μl as the threshold to initiate combined HAART (7).

Absolute mean CD4+ cell counts at initiation of HAART was 141.7 ± 176.5 cells /μl (range 1-1022) and it increased to 192.4 ± 198.5 cells /μl (3-1275) at three months. This was an increase of mean of 50.7 ± 22.0 cells/μl. Increase of CD4+ cell means in the subsequent months were 28.8, 26.0, and 21.4 cells /μl at 6th, 9th and 12th months of therapy respectively. The subsequent intervals had smaller increments that were almost similar. Similar smaller marginal increases in CD4+ cell count after initiation of highly active anti-retroviral therapy have also been noted in patients defined as incomplete responders in other studies (7-10). The mean CD4+ cell count at 12th month of therapy was 268.6 ± 189.9 (1-1390 cells /μl).

It is also noted that patients in this study who had CD4+ cell counts of ≤ 100 cells /μl at initiation of HAART had an exponential increase in CD4+ cells over the next six months of treatment compared to those with CD4+ cell counts ≥ 200 cells /μl at initiation. This has a public health importance of advocating for prompt initiation of HAART and management of opportunistic infections to save the patients from deteriorating further. As evident in this cohort, most of the patients presented late to the patient support centres for HIV care.

Seventy three (70.9%) of patients had CD4+ cell count of < 350 (60-313 cells /μl) at the 12th month of therapy despite HAART and these are considered incomplete responders (where CD4+ cell count has not normalised) with impaired immunity.

One study showed that an increase in CD4+ cell count of 99 cells / μl, in the first three months after initiating HAART in young patients, was associated with a complete response in five years. This parameter has a sensitivity and specificity of 80 and 72% respectively (baseline CD4+ / T cell count X 6-monthly CD4+ cell increase / age) (9). The initial slow increase of 50.7 ± 22.0 cells / μl in this cohort implies that the response was slow and the co-morbidities too could be one of the contributing factors, aside from therapy related factors like the type of HAART combination and adherence.

When immune recovery is impaired, even with virologically suppressive combination anti-retroviral therapy (cART), this means a longer time spent at low CD4+ cell counts, which substantially increases the risk for HIV-related morbidity and mortality (11).

Indeed variable responses in this study could be due to multiple factors including: different HAART combinations, multiple co-morbidities including opportunistic infections, severe immunosuppression as depicted by the low mean CD4+ cell count, and undetermined viral factors. Adherence was not fully evaluated but is a probable confounder. This has implication on monitoring whether to do CD4+ cell counts three-monthly or six-monthly, or initial three-monthly then six-monthly.

In this study, at the 12th month of therapy, 30 (29.1%) patients had CD4+ cell count nadir > 350 cells / μl (350-1390 cells /μl) and thus achieved immune restoration / recovery and 73 (70.9%) patients still showed inadequate immune reserve / response, CD4+ cell count < 350 cells /μl at 12th month despite HAART and are defined as incomplete responders.

Incomplete responders have been characterised by older age, more advanced HIV infection (Lower CD4+ cell count at baseline), longer duration of HIV infection and higher plasma HIV -RNA levels (10, 12). Our HIV infected patients do not access healthcare for HIV infection adequately hence they present late with advanced HIV disease.

Influence of HAART on CD4+ cell responses has been evaluated in different settings and with regard to pathophysiology and was noted to give HIV / AIDS patients better quality of life when there was a sustained HIV viral suppression (8,12-17)). Nine patients had higher CD4+ cell counts > 350 cells / μl and HAART was initiated because of their higher HIV-viral RNA load and to preserve immunity (14).

The CD4+ cell baseline level also predicts CD4+ cell response. Lower CD4+ cell counts, < 350 cells / μl was associated with a lower response to increase by 12% at four years compared to 46% response in CD4+ cell count of > 750 cells /μl at baseline. Older age groups and intravenous drug users have also been shown to be associated with lower CD4+ cell response (16).

Indeed other studies have shown that, although CD4+ cell count increases tend to be similar among patients receiving cART regimen regardless of their CD4+ cell count at baseline, patients starting cART...
with lower CD4+ cell counts are unable to reconstitute the CD4+ cell levels achieved by individuals who started anti-retroviral therapy at higher CD4+ cell counts even after three years of cART (18).

The 30 (29.1%) of patients who achieved CD4+ cell count of > 350 cells/μl at 12th month are likely to be adequately protected against opportunistic infections. Initiating HAART at CD4+ cell count > 350 cells/μl has been associated with fewer clinical events (opportunistic infections, Kaposi’s Sarcoma, thrombocytopenia, progressive multifocal leucoencephalopathy (PML), oral hairy leukoplakia, non-Hodgkins lymphoma, weight loss, herpes zoster virus, bacterial pneumonia, oral and oesophageal candidiasis, and cytomegalovirus and cervical dysplasia) during the immune reconstitution (IRIS) phase (14).

Late initiation of HAART is associated with incomplete CD4+ cell response which may affect long term prognosis, even in patients with good virologic control (8). In HAART naïve population, patients dying from HIV-1-infection are those who develop HIV-related complications before they are able to benefit from HAART-associated immune reconstitution and clinical stabilisation. This necessitates early HAART initiation.

Seventy three patients in this study were promptly initiated on HAART with in one week. Thirty patients had co-morbidities (nine severe anaemia with haemoglobin < 5.0 g/dl and required blood transfusion; 13 had elevated transaminases, AST and ALT due to HBV infection in nine of them and non-viral causes five); five had meningitis (two bacterial and three cryptococcal) and three had encephalitis and were in coma). Managing these co-morbidities delayed HAART initiation for ten to fifteen days and also dictated choice of ARTs. The associated co-morbidities including infections, as observed in this cohort, may lower the response of CD4+ cells to HAART. In this study, 73 (70.9%) patients had inadequate response with CD4+ cell counts of < 350 cells/μl at the 12th month of HAART. This compares with a study done in Paris which showed that between five and 27% of patients on HAART had low CD4+ cell counts after prolonged use of anti-retroviral drugs but successful viral suppression (18,19). Compared with control patients who had CD4+ cell counts above 500 cells/μl, and those with CD4+ cell counts less than 250 cells/μl, these patients with inadequate rise in CD4+ cell count rise had fewer naïve CD4+ T cells and lower thymic output due to thymus function impairment. They also had elevated levels of cell death by apoptosis compared to controls (17-19).

Other studies have also demonstrated that, in following up a cohort of HAART naïve HIV positive patients, the one year survival was 87% for adults and adolescents and 98% for children under 13 years of age when put on HAART treatment. Indeed, the introduction of cART in industrialised countries in 1996 dramatically reduced the risk of AIDS-defining diseases and death, saving at least three million person-years of life during the first decade of it’s use in the United States alone (21 - 23). Without treatment, one year survival averages 30% in developing countries (24,25).

A Thai study demonstrated that, even when initiated in late HIV/AIDS disease, HAART delivers clinical benefit. Mean CD4+ cell count in this study increased from 57 to 470 cells/μl over six years period in 74 patients (30). Thus, there is significant immunologic benefit associated with HAART and considerable impact on long term survival even in individuals who start HAART late and have AIDS-defining infection.

In severely immunocompromised, anti-retroviral naïve, HIV-infected patients, treatment with an efavirenz-based regimen resulted in a superior virologic response compared with a non-boosted PI-based regimen, with no difference in immunologic or clinical effectiveness (15). Patients with very low CD4+ cell counts may therefore be initiated on efavirenz based HAART regimen as a first line.

Patients in this cohort presented late as evidenced by their low mean CD4+ cell counts. Patients in resource- constrained setting present late to HIV care clinics with severe immune dysfunction, low CD4+ cell counts, multiple opportunistic infections hence require prompt HAART initiation. Increased voluntary counselling and testing (VCT) use, enhanced and sustained public health education, and expanded comprehensive care clinics (CCC) in health institutions and widespread HIV screening could help identify patients early and initiate HAART before immune depletion is severe. The provision of government - funded HAART in public hospitals being rolled out by the ministry of health will encourage patients to present for VCT and initiate HAART early. Suffice it to note that VCT centres are underutilised. Public health education and VCT use must be stepped up and sustained. There is also an urgent need to develop and incorporate simple and
sustainable strategies for initiation and delivery of HAART without delay to large numbers of patients especially in the rural areas. HAART transforms the natural course of HIV infection by reducing morbidity and mortality and increasing CD4+ counts and suppression of HIV-viral RNA (19, 23-25). But how often should CD4+ cell count be alone in public health HAART programme?

Indeed, in preventive HIV medicine, antiretroviral drugs reduce the infectivity of treated individuals by suppression of the HIV- viral load. It has been estimated in a cohort data that HAART reduces per-partnership infectivity by as much as 60% (26-29).

Question arising from this study is that should first line HAART be the same in patients with HIV infection or should it be stratified for severity especially in public health intervention? What should the minimum level of additional support coopted to public HAART programme in view of late presentation?

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