Impact of Chemotherapy on Immunological Parameters in HIV associated Malignancies

Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the requirements for the award of the degree of

D.M (ONCOLOGY)

BRANCH –VII

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

AUGUST 2011
INTRODUCTION

There are about 2.5 to 3 million HIV patients in India and the calculated prevalence in Tamilnadu is about 0.34 percent\(^1\). Survival of HIV patients has improved significantly with better control of opportunistic infections and administration of Highly Active Anti-Retroviral Therapy (HAART)\(^2\). Real incidence of AIDS-associated cancers in Indians is not known. There are only a few reports in Indian literature. It may be roughly 3-4 per cent in Indians\(^2\),\(^3\).

Since the onset of the HIV/AIDS pandemic in the early 1980s, HIV infection and cancer have been closely related. Several reasons explain this phenomenon; the immune suppression induced by HIV favors occurrence of cancers such as high-grade non-Hodgkin’s lymphoma (NHL); the oncogenic nature of certain viruses, which directly cause cancers such as HHV8 and Kaposi’s sarcoma (KS) and human papilloma virus and cervical cancer in women or rectal squamous cell cancer in men. Because many of these tumors have such a high prevalence in HIV-infected persons, they are included as part of the clinical definition of AIDS and are reported formally as “AIDS-defining malignancies”. Secondly, the increase in survival of HIV-infected patients has led to the observation in several cohort studies that an increasing number of “non-AIDS-defining malignancies”, such as Hodgkin’s disease (HD), invasive anal carcinoma, lung carcinoma, skin cancer and hepatocarcinoma, are now
being reported at higher than expected frequencies compared to rates observed in the general population.

The hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as helper T cells. This subset of T cells is defined phenotypically by the presence on its surface of the CD4 molecule which serves as the primary cellular receptor for HIV. It has been observed that malignancies may be related to two different profiles: time spent with a low CD4 cell count and exposure to a high viral load\(^4\). Both conditions are associated with a higher risk for developing AIDS-related cancers while the time spent with CD4 counts under 500 cells/mm\(^3\) or with viral load greater than 500 copies/ml are associated with a higher risk for non-AIDS-defining malignancies\(^5\).

In the pre-HAART era, treatment for HIV associated Malignancy mandated risk assessment, comparing the chance of successful therapy against the possibility of worsening severe immunodeficiency leading to mortality. A variety of treatment approaches were evaluated including standard-dose, reduced-dose, and even escalated dose chemotherapy\(^6,7,8,9\). Outcomes were poor regardless of treatment choice with complete response rates of about 50% and median survivals in the 5 to 8 month range\(^6,7,8\).
The optimal management of HIV associated Malignancies is challenging since we have to deal with the immune compromise associated with HIV and the natural history, clinical features and associated complications arising due to the primary tumor – both solid and hematological malignancies – including tumor site, nodal and metastatic stage.

Implementation of highly active antiretroviral therapy (HAART) has changed the epidemiology, clinical outcome and therapeutic approach of HIV-associated malignancies. The use of concomitant chemotherapy and HAART has been demonstrated to be feasible and effective in reducing morbidity associated with opportunistic infections and to improve overall survival in patients with HIV-related malignancies\textsuperscript{10,11}.

At the department of Medical Oncology, Madras Medical College, Chennai, about 2200-3000 new patients are registered annually. Of these, the incidence of HIV and Malignancy has not been evaluated but it has been observed that there is a noticeable increase in the incidence in the past few years.
Patients infected with human immunodeficiency virus (HIV) are at a significantly increased risk of developing cancer compared with the general population. In fact, the onset of the acquired immune deficiency syndrome (AIDS) epidemic was heralded by an increased incidence of a rare malignancy, Kaposi’s sarcoma (KS), in 1981\(^{12,13}\). In 1982, the U.S. Centers for Disease Control and Prevention (CDC) proposed the initial case definition for AIDS, including such AIDS-defining malignancies as KS and primary central nervous system lymphoma (PCNSL)\(^{14}\). Subsequent revisions of the CDC definition for AIDS resulted in the addition of non-Hodgkin’s lymphoma (NHL) not restricted to the CNS\(^{15}\) and invasive cervical cancer\(^{16}\).

In addition to the aforementioned AIDS-defining malignancies, patients infected with HIV are also at increased risk for developing certain non-AIDS-defining cancers. In large database studies of linked AIDS and cancer registries, the overall rates of several neoplasms including Hodgkin’s lymphoma, invasive anal carcinoma, multiple myeloma, leukemia, lung cancer, as well as malignancies involving the oral cavity, lip, esophagus, stomach, liver, pancreas, larynx, heart, vulva, vagina, kidney, and soft tissues (e.g., leiomyosarcoma in children), were found to be in excess in patients infected with HIV\(^{17-20}\). However, unlike the AIDS-defining malignancies, the association of many of these non-AIDS-defining
cancers with progressive immunosuppression has not been established \textsuperscript{17-21}. Other oncogenic mechanisms are therefore likely involved, including confounding epidemiologic associations (e.g., smoking) or viral co-infections (e.g., human papilloma virus). The most common epithelial cancers found in the general population do not appear to occur more frequently in HIV-positive patients, including carcinoma of the breast, prostate, and colon \textsuperscript{17, 18, 20, 21}.

With the advent of highly active antiretroviral therapy (HAART), the morbidity and mortality associated with HIV infection dramatically improved \textsuperscript{22}. As a result of the immune reconstitution afforded by effective combination antiretroviral therapies, the epidemiological and clinical profile of cancers in the setting of HIV infection also changed. While significant decreases in certain AIDS-defining cancers such as KS have been reported, similar declines for other malignancies such as AIDS–related lymphoma (ARL) are less evident \textsuperscript{22, 23}. Moreover, with patients now living longer with chronic HIV infection and sustaining fewer opportunistic infections in the HAART era, malignancy in this population is becoming an increasingly prominent cause of death in the later stages of AIDS \textsuperscript{5, 24}. Despite the emergence of AIDS-related cancers in the HAART era, concomitant advances in chemotherapy, antiretroviral drugs, and supportive care protocols are allowing for more aggressive
management of AIDS-related cancers compared with the pre-HAART years\textsuperscript{25}.

The role of CD4+ cell count and HIV-1 RNA level in the incidence and outcome of nADCs remains unknown. However, D:A:D cohort investigators reported that a low CD4+ cell count is a strong independent risk factor for death attributable to both ADC and nADC\textsuperscript{26}. The D:A:D investigators also found that age and long–term HAART use are associated with increased risk of death attributable to nADCs. These results were confirmed by similar findings in the French ONCOVIH study, which found that CD4+ cell count and HIV-1 RNA level predicted risk of nADC\textsuperscript{27} and in a British cohort study, which found that NNRTI exposure and low nadir CD4+ cell count are associated with increased risk of nADCs\textsuperscript{28}.

Crum-Cianflone and colleagues\textsuperscript{2} analyzed incidence of ADC and nADC during 4 clinical periods: - the early pre-HAART era (1984-1990), - the late pre-HAART era (1991-1995), - the early post-HAART era (1996-2000), and - the late post-HAART era (2001-2006). The investigators concluded that the incidence of Non-AIDS–Defining cancers was increasing, constituting majority of cancer cases despite the use of HAART. The investigators also assessed whether CD4+ cell count, HIV-1 RNA level, and antiretroviral exposure predicted cancer occurrence. This was a retrospective analysis of US military beneficiaries benefits from 23 years
of follow-up (33,486 person-years) on 4498 HIV-infected individuals. However, this is a very distinct population, notable for free access to health care, geographic variability, stable health insurance over many years, early diagnosis of HIV because of routine screening, and unique demographics (median 28 years of age at HIV diagnosis, 91.0% male, 43.5% white, 45.3% black, and 76.6% of HIV diagnoses before 1996). The investigators did not report the mode of HIV exposure.

A shortcoming of this analysis was the absence of HIV-1 RNA from the multivariate analysis because 28% of patients did not have HIV-1 RNA data (probably because 68% of the cancers developed in the pre-HAART era). Nadir CD4+ cell count was also not analyzed or reported. Other unreported and unanalyzed data include hepatitis B and C co-infection, smoking rate, alcohol use, and injection drug use. This unique cohort allowed for detailed and complete follow-up of patients before and after cancer diagnosis. However, results from this study may be difficult to generalize to other HIV patient groups.

With those limitations in mind, this cohort study yielded several notable findings. First, as noted above, the majority (68%) of the cancers developed in the pre-HAART era. The rate of ADCs peaked during the late pre-HAART era at 14.2 (per 1000 person-years) and declined to 5.4 in the early post-HAART era and to 2.7 in the late post-HAART era. The opposite was true for nADCs (including skin cancers), which have
risen in recent years: 2.9 in the early pre-HAART era, 2.8 in the late pre-HAART era, 4.2 in the early post-HAART era, and 6.7 in the late post-HAART era. Overall, the proportion of cancers classified as nADCs increased from 20% in the pre-HAART era to 71% in the late post-HAART era (P < .0001).

These trends are confirmed by individual cancers in each category (Kaposi’s sarcoma and non-Hodgkin’s lymphoma among ADCs, and anal, prostate, renal, and Hodgkin’s disease among nADCs) but with small sample sizes (except for anal carcinoma with a significant 13-fold increase over the study period; P = .001). Notably absent were large numbers of lung cancer and liver cancer, two problematic cancers in most other non-HIV cohorts.

Not surprisingly, ADCs were associated by multivariate analysis with a non cancer AIDS diagnosis, lower CD4+ cell counts, higher HIV-1 RNA levels, and lack of HAART. Older age at HIV diagnosis was significantly associated with increased risk of ADCs by univariate analysis and even more strongly associated with nADCs (hazard ratio: 2.15/10 years for nADC; hazard ratio: 1.25/10 years for ADC). These findings confirmed results of other cohort studies28,29,30.

It was also seen that CD4+ cell counts at ADC diagnosis rose substantially (but not significantly) during the 4 study periods, with
medians of 40, 80, 44, and 242 cells/mm³, respectively (P = .14). This is an interesting trend for practitioners who are finding that ADCs occur at higher CD4+ cell counts in the current era probably because of a shift from Kaposi’s sarcoma and primary central nervous system lymphoma to non-Hodgkin’s lymphoma. However, two recent reports described substantial Kaposi’s sarcoma disease among patients with high CD4+ cell counts receiving HAART 31,32. Among nADCs, no association was found between CD4+ cell count, HAART use, or prior non cancer AIDS diagnoses - a finding that contradicts results of the ONCOVIH study 27 and a report by Powles and colleagues 28. But these new results are limited by the small number of non-skin cancer nADCs in the study 2.

**Definition**

The current CDC classification system for HIV-infected adolescents and adults categorizes persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts. The system is based on three ranges of CD4+ T lymphocyte counts and three clinical categories and is represented by a matrix of nine mutually exclusive categories (Table 1).
TABLE 1

<table>
<thead>
<tr>
<th>CD4+ T Cell Categories</th>
<th>Clinical Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A - asymptomatic, Acute (Primary) HIV or PGL</td>
</tr>
<tr>
<td>&gt;500/microL</td>
<td>A1</td>
</tr>
<tr>
<td>&lt;200/microL</td>
<td>A3</td>
</tr>
</tbody>
</table>

TABLE 2

**Category A:** Consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in categories B and C must not have occurred.

Asymptomatic HIV infection

Persistent generalized lymphadenopathy

Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

**Category B:** Consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and that meet at least one of the following criteria: (1) The conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or (2) the conditions are considered by physicians to have a clinical course or to require management that is complicated by
HIV infection. Examples include, but are not limited to, the following:

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tuboovarian abscess
- Peripheral neuropathy

**Category C**: Conditions listed in the AIDS surveillance case definition.

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus disease (other than liver, spleen, or nodes)</td>
</tr>
<tr>
<td>Cytomegalovirus retinitis (with loss of vision)</td>
</tr>
<tr>
<td>Encephalopathy, HIV-related</td>
</tr>
<tr>
<td>Herpes simplex: chronic ulcer(s) (&gt;1 month's duration); or bronchitis, pneumonia, or esophagitis</td>
</tr>
<tr>
<td>Histoplasmosis, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>Isosporiasis, chronic intestinal (&gt;1 month's duration)</td>
</tr>
<tr>
<td>Kaposi's sarcoma</td>
</tr>
<tr>
<td>Lymphoma, Burkitt's (or equivalent term)</td>
</tr>
<tr>
<td>Lymphoma, primary, of brain</td>
</tr>
<tr>
<td><em>Mycobacterium avium</em> complex or <em>M. kansasii</em>, disseminated or extrapulmonary</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em>, any site (pulmonary or extrapulmonary)</td>
</tr>
<tr>
<td><em>Mycobacterium</em>, other species or unidentified species, disseminated or extrapulmonary</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em> pneumonia</td>
</tr>
<tr>
<td>Pneumonia, recurrent</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td><em>Salmonella</em> septicemia, recurrent</td>
</tr>
<tr>
<td>Toxoplasmosis of brain</td>
</tr>
</tbody>
</table>
Using this system, any HIV–infected individual with a CD4+ T cell count of <200/microL has AIDS by definition, regardless of the presence of symptoms or opportunistic diseases (Table 2). Once individuals have had a clinical condition in category B, their disease classification cannot be reverted back to category A, even if the condition resolves; the same holds true for category C in relation to category B\textsuperscript{33,34}.

All malignancies are grouped under category C. They may have any CD4+ count at presentation. Here in comes the question when and how to start HAART along with chemotherapy and prophylactic antibiotics.

**When to Start Antiretroviral Therapy**

The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection\textsuperscript{34,35,36}. This measurement, which can be made directly or calculated as the product of the percent of CD4+ T cells (determined by flow cytometry) and the total lymphocyte count has been shown to correlate very well with the level of immunologic competence. Patients with CD4+ T cell counts <200/microL are at high risk of disease from *P. jiroveci*, while patients with CD4+ T cell counts <50/microL are at high risk of disease from CMV, mycobacteria of the *M. avium* complex (MAC) and/or *T. gondii*. Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every
3–6 months thereafter. More frequent measurements should be made if a declining trend is noted.

According to most guidelines, a CD4 T cell count <350/microL is an indication for consideration of initiating ARV therapy, and a decline in CD4+ T cell count of >25% is an indication for considering a change in therapy. Once the CD4+ T cell count is <200/microL, patients should be placed on a regimen for *P. jiroveci* prophylaxis, and once the count is <50/microL, primary prophylaxis for MAC infection is indicated.

CIPRA HT-00137 and SMART and other randomized trials study showed a trend of lower risk of serious AIDS- and non-AIDS-related events in those who initiated therapy immediately compared with those who deferred therapy until CD4 count dropped to <250 cells/mm3 (p = 0.06). Collectively, these studies support the recommendation that ART should be initiated in patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm3.

The incidence of non-AIDS malignancy in HIV-infected subjects is higher than in matched HIV-uninfected controls. Large cohort studies of mostly patients receiving ART have reported a consistent link between low CD4 counts (<350–500 cells/mm3) and the risk of AIDS and/or non-AIDS-defining malignancy. The ANRS C04 Study demonstrated a
statistically significant relative risk of all cancers evaluated (except for anal carcinoma) in patients with CD4 counts <500 cells/mm³ compared with patients with current CD4 counts >500 cells/mm³ and a protective effect of ART for HIV-associated malignancies. This potential effect of HIV-associated immunodeficiency is particularly striking with regard to cancers associated with chronic viral infections (e.g., HBV, HCV, human papilloma virus [HPV], Epstein-Barr virus [EBV], human herpes virus-8 [HHV-8]). Cumulative HIV viremia itself may also be associated with the risk of non-Hodgkin lymphoma and other AIDS-defining malignancies, independent of other factors. Together this evidence suggests that initiating ART to suppress HIV replication and maintain CD4 counts at above 350–500 cells/mm³ may reduce the risk of both AIDS-defining and non-AIDS-defining malignancies.

**Randomized Trials in HIV Associated Malignancies**

Prior to the advent of HAART, patients with AIDS-related NHL were managed with low-dose regimens due to concerns of unacceptable toxicity. Survival at 2 years was approximately 10%.

With the advent of HAART, groups began combining HAART with cytotoxic chemotherapy. The first report of a series including patients treated with chemotherapy and HAART described an alternating weekly chemotherapy regime using bleomycin, etoposide, vincristine, methotrexate,
prednisolone/cyclophosphamide, doxorubicin (BEMOP/CA) in patients with a good prognosis. Around half of these patients were receiving HAART, and the overall 2-year survival rate was 46\%(95\% CI27\%–65\%), with a 2-year lymphoma-specific survival of 59\%(95\%CI 27\%–65\%) \(^{57}\).

The feasibility of combining chemotherapy with HAART therapy was formally explored in the AIDS Malignancy Consortium005(AMC005) trial, which compared CHOP chemotherapy at a reduced dose (mCHOP) or full-dose CHOP, with concomitant HAART therapy (stavudine, lamivudine, and indinavir) being given to all patients \(^{58}\).

They reported overall response rates for mCHOP and full-dose CHOP of 60\% (95\% CI45\%–75\%) and 57\% (95\% CI38\%–77\%), respectively \(p=0.79\), although the complete response rate was significantly higher in the full-dose CHOP arm (48\%, as compared to 30\% in mCHOP). No long-term outcome data have been reported for this group of patients. There were no significant differences in grade 3 and 4 toxicities observed in the two groups. Furthermore, HIV viral loads declined and CD4 counts increased significantly despite the concurrent use of chemotherapy.
## TABLE 3

Summary of published phase II/III trials in the post-HAART era

<table>
<thead>
<tr>
<th>Chemotherapy Regimen (reference)</th>
<th>N</th>
<th>Receiving HAART</th>
<th>Complete response rate</th>
<th>Median survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose m-BACOD (^9)</td>
<td>98</td>
<td>Optional</td>
<td>41%</td>
<td>35weeks (95% CI 30–45%)</td>
<td>1year:27% 2year:11%</td>
</tr>
<tr>
<td>Standard dose m-BACOD (^9)</td>
<td>94</td>
<td>Optional</td>
<td>52%</td>
<td>31weeks (95% CI 22–42%)</td>
<td>1year:24% 2year:7%</td>
</tr>
<tr>
<td>BEMOP-CA (^57)</td>
<td>30</td>
<td>50%</td>
<td>60%</td>
<td></td>
<td>2year:46% (95%CI27–65%)</td>
</tr>
<tr>
<td>CHOP mCHOP (^58)</td>
<td>25</td>
<td>100%</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP (^59)</td>
<td>17</td>
<td>100%</td>
<td>75%</td>
<td></td>
<td>2year probability: 0.59(95%CI0.31–0.87)</td>
</tr>
<tr>
<td>CHOP m-BACOD MA-COP-B ACVB (^60)</td>
<td>44</td>
<td>82%</td>
<td>52% HAART responders:71%</td>
<td>360days, HAART-treated: 425days (95%CI241–609)</td>
<td>1year(cumulative probability):0.49 HAART-treated:0.51 Virological response to HAART:0.84</td>
</tr>
<tr>
<td>Treatment</td>
<td>Weeks</td>
<td>CR</td>
<td>PR</td>
<td>1 year</td>
<td>2 year</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------</td>
<td>-----</td>
<td>-----</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>CHOP 61</td>
<td>24</td>
<td>100%</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA-EPOCH 62</td>
<td>39</td>
<td>0</td>
<td>74%</td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(at median follow-up of 53 months)</td>
</tr>
<tr>
<td>CDE 63,64</td>
<td>55</td>
<td>100%</td>
<td>44%</td>
<td>13.7 months</td>
<td>1 year:57%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 year:45%</td>
</tr>
<tr>
<td>CHOP (Liposomid alox) 65</td>
<td>24</td>
<td>100%</td>
<td>75%</td>
<td>413.4 months</td>
<td>1 year:58%</td>
</tr>
<tr>
<td>CDE + rituximab 66</td>
<td>74</td>
<td>76%</td>
<td>70%</td>
<td></td>
<td>2 years (estimated): 64%</td>
</tr>
<tr>
<td>CHOP 67</td>
<td>50</td>
<td>100%</td>
<td>47%</td>
<td>110 weeks</td>
<td>NS</td>
</tr>
<tr>
<td>CHOP + rituximab</td>
<td>99</td>
<td>100%</td>
<td>58%</td>
<td>139 weeks</td>
<td>NS</td>
</tr>
<tr>
<td>CHOP/ACVB-P 68</td>
<td>35</td>
<td>100%</td>
<td>54%</td>
<td>22 months</td>
<td>1 year:54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 year:49%</td>
</tr>
</tbody>
</table>

These data were supported by a further study which looked at the effect of HAART on the response to treatment and survival in patients with HIV-associated NHL treated with CHOP chemotherapy, using historical controls. This revealed that patients treated with CHOP plus HAART had a higher response rate than those treated with CHOP alone (75% vs. 34%; p = 0.003) 69. Other studies involving CHOP given with HAART have reported response rates of 47–75%, with median survival
of 27 months and overall survival of 58% and 55% being reported at one and two years, respectively \(^61,65,67\). The substitution of liposome-encapsulated doxorubicin for conventional doxorubicin in the CHOP regimen does not appear to affect the efficacy of this treatment \(^65\).

A prospective observational study of 44 patients included 34 treated with CHOP and the remaining 10 with either m-BACOD, modified m-BACOD, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin (MA-COP-B) or adriamycin, cyclophosphamide, vinblastine, and bleomycin (ACVB). Eight patients in this cohort did not take HAART. The study reported a complete response in 52% of patients, with a complete response more frequently seen in those who had a virological response to HAART (70% as opposed to 30% in non-responders. Multivariate analysis revealed that virological response to HAART was the only variable associated with tumour response (OR 6.36, 95% CI 1.56–25.81) \(^60\). This finding could be related to the fact that those who had a virological response received a significantly higher dose intensity of chemotherapy, compared to those who did not respond to HAART, due to the possible improvement in haematopoiesis given the inhibition of HIV. This enabled a greater dose density of chemotherapy to be delivered, which is a known factor in the outcome of NHL. The estimated overall survival for all patients was 360 days (95% CI 81–639), with a 1 year cumulative survival probability of
0.49; however, in the HAART-treated patients, estimated overall survival was 425 days (95% CI 241–609), with a 1 year cumulative probability of 0.51, increasing to 0.78 in those with a virological response to HAART. 

Preclinical data suggested that infusional schedules of cytotoxic agents might have a therapeutic advantage. Two infusional chemotherapy regimens have been investigated in AIDS-related NHL, namely: cyclophosphamide, doxorubicin and etoposide (CDE) administered as a 96-h continuous infusion, and cyclophosphamide, doxorubicin, etoposide, vincristine and prednisolone (EPOCH). CDE was first found to be highly active and capable of producing durable remissions in HIV-related NHL in a small pre-HAART era study. In this study, CDE was administered to 12 HIV-sero positive and two HTLV-1-seropositive patients. A complete response rate of 71% and a partial response rate of 21% was observed. Median survival was estimated at 17.4 months, with seven of the 12 HIV-positive patients alive and disease-free at a median follow-up of 15 months. A subsequent report of 25 patients with AIDS-related lymphomas treated with CDE plus didanosine produced a complete response rate of 58% (95% CI 38–78%) and a median survival of 18.4 months; this was seen as a major advance in the treatment of HIV related NHL. The same schedule combined with saquinavir produced similar results. A comparison of patients treated with CDE revealed improved overall survival with the concurrent use of HAART as compared to those
in the pre-HAART group, namely those patients treated with didanosine (p=0.039). Complete response rates of 50%, with a 2-year survival of 61% and median survival of 26 months, have been reported by others using this regimen.

**Treatment of HIV-associated NHL with omission of HAART**

Dose-adjusted EPOCH (DA-EPOCH; etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen is an infusional regimen developed from in vitro studies showing that tumor cells are relatively less resistant to prolonged low concentration exposure to the natural product derived agents vincristine, doxorubicin, and etoposide, compared with brief higher concentration exposure. Clinically, DA-EPOCH can overcome resistance to standard CHOP chemotherapy. A study of DA-EPOCH in 50 untreated HIV-negative patients with diffuse large B-cell lymphomas (DLBCLs) showed an overall and progression-free survival of 73% and 0%, respectively, at 5 years. The dose-adjustment strategy was developed to reduce hematopoietic toxicity while maintaining maximum dose intensity by normalizing drug doses to the absolute neutrophil nadir.

The rationale behind interrupting HAART was to avert adverse drug reactions that could reduce the chance of cure. In addition, it was felt firstly that HAART would not prevent chemotherapy-induced lymphocyte
depletion, secondly that the predicted HIV dependent CD4+ cell loss during the 16-week period of HAART would be relatively small, and thirdly there was concern that HAART could inhibit lymphocyte apoptosis, and hence impact on the efficacy of chemotherapy\textsuperscript{74}. Other potential reasons to consider omission of HAART for patients receiving chemotherapy included compliance issues in the setting of polypharmacy, as well as problems with chemotherapy-induced nausea, vomiting and mucositis which may reduce ability to comply with treatment\textsuperscript{75,76}.

A complete response was achieved by 29 patients (74%; 95% [CI]:58-87) and a partial response was achieved by 5 patients (13%), for a total response rate of 87%. Among patients with CD4+ cells more than 100/mm\textsuperscript{3}, 87% achieved a complete response, whereas 56% of patients with lower CD4+ cell counts achieved a complete response. At the median potential follow-up of 53 months, the progression-free survival was 73% and the overall survival was 60%. When analyzed by CD4+ cell number ( < or > 100cells/mm\textsuperscript{3}), the overall survival rates were 16% and 87%, respectively, at 53 months. CD4 cells decreased to a median of 189 cells/mm\textsuperscript{3}(range: +19 to -973) by cycle 6, followed by recovery to baseline within 6 to 12 months\textsuperscript{77}.

Dose adjustment with antiretroviral suspension allowed full delivery of the infused agents, while minimizing clinical and immune toxicity.
Treatment was well tolerated and the incidence of serious adverse effects was similar to standard CHOP chemotherapy.

These results also raised challenging questions about the role of HAART during the treatment of ARL. It is commonly held that HAART is necessary to prevent uncontrolled HIV replication and loss of immune function during chemotherapy. A recent study suggested that response to HAART is essential to treat ARL with curative intent\textsuperscript{60}. However, the study found that antiretroviral therapy is not required during chemotherapy to achieve a high overall survival and post-treatment viral control and immune recovery. Only the CD4+ cell counts and involvement of the central nervous system at study entry were independent prognostic factors in the study, both of which are interrelated with the tumor pathobiology\textsuperscript{78,79,80}.

**Role of rituximab in the treatment of HIV-associated NHL**

The addition of rituximab (R) substantially improves response and progression-free survival in ARL, although in a randomized trial comparing CHOP with R-CHOP, these improvements were not statistically significant. Around 14% of patients receiving rituximab died of treatment-related infectious deaths, annulling any advantage to overall survival\textsuperscript{67}. Yet, this trial documented a complete response rate that was 22% higher in the group that
received R-CHOP. Moreover, only 8% of the group that received R-CHOP had disease progression, compared with 21.6% of those receiving CHOP alone.\textsuperscript{81}

A more recent phase II trial of R-CHOP in ARL found that there was no excess toxicity and documented a complete response rate of 77% and a 2-year survival rate of 75%\textsuperscript{82}. Three phase II trials of rituximab with CDE (continuous infusion during 96 hours of cyclophosphamide, doxorubicin, and etoposide), showed a complete response rate of 70% and both disease-free and overall survival of 55% at a median follow-up of 23 months was documented\textsuperscript{82}. A phase II randomized trial of either R-dose adjusted (DA)-EPOCH (rituximab given with 96 hours of continuously infused etoposide, doxorubicin, and vincristine with oral prednisone and bolus cyclophosphamide dose-adjusted for tolerance) or DA-EPOCH followed by rituximab maintenance indicates a 1-year progression-free survival of 80% in the R-DA-EPOCH arm and 72% in the arm of DA-EPOCH followed by rituximab\textsuperscript{83}. There were no excess treatment-related complications. This latter study appeared to confirm the findings of a phase II trial of DA-EPOCH alone that reported a complete response rate of 74% and a disease-free survival and overall survival 92% and 60%, respectively, at a median follow-up of 53 months\textsuperscript{77}.

**CD4 cell dynamics and chemotherapy**

The effect of chemotherapy on CD4 count and plasma HIV viral load has been investigated in some clinical trials. The results reported vary; some
studies have found an increase in the CD4 count on treatment (e.g. from a median baseline value of 138 (CHOP) and 122 (mCHOP) cells/mm$^3$ to a median of 216 cells/mm$^3$ after treatment$^{58}$. In contrast, two other trials of chemotherapy alone found a decrease in CD4 cell count with treatment, with a mean change between commencement and completion of 47 cells/mm$^3$ $^{60}$ and a 50% decrease in another$^{84}$. In the CHOP and mCHOP trial, there were no differences in the CD4 and VL dynamics between the two chemotherapy arms$^{58}$. With DA-EPOCH where HAART is discontinued, the CD4 count decreased by a median of 189 cells/mm$^3$ (range +19 to -973) by the sixth cycle of treatment$^{62}$.

Only one trial that combined chemotherapy and Rituximab has described CD4 and viral load changes. It showed a small drop in the median CD4 count between baseline and one month post treatment, from 161/mm$^3$ to 108/mm$^3$.

**Non–AIDS-Defining Cancers in the Era of HAART**

Non AIDS defining cancers have increased in the era of HAART. Although it may be premature to consider this an epidemic of cancer in HIV/AIDS, several factors suggest that the incidence of non AIDS-defining cancer in HIV/AIDS is likely to increase. The excess risk of certain non AIDS-defining cancer is partly attributable to other risk factors for these tumors in HIV-infected patients, such as cigarette smoking. However, the risk of these
non AIDS-defining cancers does not appear to be fully explained either by these cofactors or HIV-related CD4 cell depletion. For example, the nearly fivefold excess lung cancer risk in HIV appears related to age and HAART use, but not to CD4 cell count, and the risk remains elevated at 2.5-fold more than the general population, even when adjusted for smoking. Standardized to the background population the incidence for Hodgkin's lymphoma (HL) is also increasing in populations in which HAART is commonly available, increasing from eightfold to nearly 14-fold the expected incidence since HAART became available. Indeed, recent studies indicate that cancer is now the most common cause of death in patients with HIV infection, and about half of these cancer-associated deaths are caused by AIDS-defining malignancies and about half by non AIDS-defining cancer.

No randomized studies have addressed the question of the best chemotherapy regimen for patients with nADC and HIV infection, and the data are derived mainly from non-randomized controlled trials or case series.

Hodgkin's lymphoma, anal cancers, germ cell tumors, NSCLC, HCC treatment are recommended according to British HIV Association Guidelines. There are no specific guidelines for tumors of breast, head and neck, melanoma, colon and other urological sites.

For anal cancer, in phase II studies in HIV-positive individuals, the best outcomes appear to have derived from the use of combined modality therapy of
radiotherapy and concurrent chemotherapy. This generally has involved 5-fluorouracil and mitomycin C, and concomitant radical radiotherapy to the pelvis (38-51 Gy in 20-30 fractions), with most patients receiving a perineal boost (10-18 Gy). There is no evidence that HAART can cause regression of anal cancer, but we recommend its use to prevent other infections, maintain CD4 cell count and suppress viraemia.

For Hodgkins lymphoma the recommendations are that all patients should be treated with HAART (level of evidence III B).

First-line treatment: standard chemotherapy (ABVD) should be offered (level of evidence III b). More intensive chemotherapies (BEACOPP or Stanford V) might be considered in the context of a clinical trial (level of evidence III C).

Second-line treatment: salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation should be strongly considered unless the patient has multiclass-resistant HIV with no remaining antiretroviral options (level of evidence III B).

**HIV Associated Malignancies: Do we need HAART**

A roundtable discussion convened at the Ninth International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies recommended that if a patient is tolerating a stable HAART regimen, it may be
reasonable to continue this during chemotherapy\textsuperscript{56}. This panel also noted that it may be advisable to wait until after chemotherapy is completed for patients not already receiving antiretroviral therapy.

**Rationale of the proposed study**

This study is built upon the evidence that HAART along with chemotherapy is the standard of care in HIV associated malignancies and standard dose of chemotherapy can be given. By the proposed study, the following objectives are being tested:

1. CD4+ count during chemotherapy may vary and correlating it to response rate.

2. An increase in CD4+ Count will result in decreased opportunistic infections and chemotherapy related toxicities.
AIM OF THE STUDY

To evaluate the impact of chemotherapy and HAART on immunological parameters in all HIV associated malignancies.

1. To describe the response after each cycle of chemotherapy and HAART with reference to CD4 count.

2. To study the pattern of HIV patients presenting with AIDS defining cancers and non-AIDS defining cancers.

3. To determine the feasibility of treatment delivery, patient tolerance, and acute toxicities.
MATERIALS AND METHODS

PATIENT SELECTION

1. Conditions for patient eligibility

1.1 Pathologically (histologic or cytologic) proven diagnosis of primary solid or hematological malignancy and metastasis of unknown origin.

1.2. Serologic proof of HIV (ELISA/TRIPLE RAPID TEST).

1.3. All Stages of malignancy based upon the following minimum diagnostic work-up:

1.3.1. History / physical examination within 4 weeks prior to registration.

1.3.2. Imaging work-up with chest roentogram, usg –abdomen/ pelvis/scrotum within 4 weeks prior to registration.

1.3.3. Chest/abdomen/brain/whole neck –CT or MRI wherever feasible within 4 weeks prior to registration.

1.3.4. ECG/ECHOCARDIOGRAM within a week prior to registration.

1.3.5. Endoscopy –upper or lower GI Scopy, Bronchoscopy whenever necessary within 4 weeks prior to registration.
1.3.6. Peripheral smear and bone marrow biopsy/smear whenever necessary within a week prior to registration.

1.4. Zubrod/ ECOG performance status 0-2.

1.5. Age: Above 10 and below 65.

1.6. CBC/differential obtained within a week prior to registration on study, with or without bone marrow involvement but with adequate bone marrow function defined as follows:

1.6.1. Absolute neutrophil count (ANC) $\geq 1500$ cell/mm$^3$.

1.6.2. Platelets $>100000$ cells/mm$^3$. (Note:The use of transfusion or other intervention to achieve platelets $>100000$/mm$^3$ is acceptable)

1.6.3. Hemoglobin $>8.0$g/dl. (Note:The use of transfusion or other intervention to achieve Hgb $>8.0$g/dl is acceptable).

1.7. Additional laboratory studies obtained within 2 weeks prior to registration on study

1.7.1. Creatinine $<1.5$mg/dl

1.7.2. Bilirubin $<1.5$ x upper limit of normal.

1.7.3. AST $<3$x upper limit of normal.

1.7.4. Serum pregnancy test for women of childbearing potential.
1.7.5. Serum lactate dehydrogenase (LDH)

1.8. HBsAG and HBC within 4 weeks prior to registration on study.

1.9. Patient must provide Signed study-specific consent form prior to study entry.

2. Conditions for patient ineligibility

2.1. Malignancy confirmed patients but serologically negative for HIV.

2.2. No prior chemotherapy for malignancy

2.3. No prior radiation therapy

2.4. Prior allergic reaction to the study drugs involved in this protocol.

2.5. Severe, active medical comorbidity defined as follows

2.5.1. Unstable angina and/or congestive heart failure requiring hospitalization within the last 3 months

2.5.2. Transmural myocardial infarction within the last 6 months.

2.5.3. Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration.
2.6. Pregnant women and nursing mothers and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be teratogenic.

2.7. Age above 65 years.

2.8. Post transplant patients because the natural history and treatment modality may be different.

**METHODOLGY**

All patients referred to our department with known HIV positivity and patients without known HIV status are referred for Elisa/Triple rapid test and are included in our protocol study.

All HIV Positive patients are then registered with ART centre and assessed for CD4 count routinely and viral load if possible. This study requires only CD4 count done at the time of registration and at the beginning of next chemotherapy. Staging of HIV infection was done with CD4+ counts. Serum LDH was estimated for evaluation of disease activity. Patient and relatives were given complete information about the nature of both the diseases, further plan of management and complications involved in this. Different treatment options of highly active anti-retroviral therapy (HAART) were discussed with patients. Reverse transcriptase inhibitor (RTI) – or protease inhibitor (PI) based
antiretroviral therapy, interaction between chemotherapeutic agents, their toxicities were discussed in detail with the patient and relatives.

**PRETREATMENT EVALUATIONS**


2. All patients evaluated by a medical oncologist prior to study.

3. Laboratory studies –within a week prior to treatment

   3.1. CBC

   3.2. Renal and liver parameters, LDH, Alkaline phosphatase, URIC acid, calcium, phosphorous, magnesium.

4. Peripheral smear and bone marrow biopsy/smear in all hematological and small round cell solid tumors.

5. Imaging studies-within 4 weeks prior to study

   - CT SCAN of brain, neck, chest and abdomen, spine and limbs wherever necessary.

   - Upper/lower GI endoscopy

   - Chest X ray
-All other data to stage malignancy with TNM classification or ANN ARBOR or other staging with respect to the disease concerned.

6. Biopsy /cytology of the primary tumor

7. Specific serum tumor markers to diagnose, stage, prognosticate and follow-up.

8. Immunohistochemistry / Flow cytometry to confirm and subtype hematological malignancy.


10. HIV status confirmation and CD4 count.

**TREATMENT : HAART**

According to the operational guidelines of NACO, the patients are initiated on HAART when the CD4 count is less than 200 or in severe/advanced symptoms irrespective of CD4 count. All malignant patients are hence defined as advanced symptoms and are started on HAART.

Principles for selecting the first-line regimen

1. Choose 3TC (lamivudine) in all regimens

2. Choose one NRTI to combine with 3TC (AZT or d4T)

3. Choose one NNRTI (NVP or EFV)
Fixed-dose combinations (FdCs) are preferred because they are easy to use, improve adherence to treatment and thus reduce the chances of development of drug resistance. The current national experience shows that bid (twice a day) regimens of FDCs are well tolerated and complied with.

**Preferred first line regimen:**

Zidovudine (300 mg) + lamuvidine (150 mg) + Nevirapine(200 mg). Zidovudine may cause anaemia, which requires Hemoglobin monitoring, but is preferred over Stavudine because of its toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy). Patients who develop severe anaemia while on an Zidovudine based regimen should not be re-challenged with Zidovudine. In such cases, the patient should receive either Stavudine or Tenofavir (in place of Zidovudine).

**Alternative first line regimens**

1) Zidovudine (300 mg) + Lamivudine (150 mg) + Efavirenz (600 mg). Efavirenz is substituted for Nevirapine in cases of intolerance to the latter or if patients are receiving rifampicin containing anti-TB treatment. Efavirenz should not be used in patients with grade 4 or higher elevations of ALT.

2) Stavudine (30 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)/ Efavirenz (600 mg). If the patients have anaemia, Stavudine based regimen should be prescribed.
TREATMENT: CHEMOTHERAPY

Treatment of malignancies is site-specific and guided by institutional protocol.

1. Non Hodgkins Lymphoma: Cyclophosphmaide, adriamycin, vincristin, prednisolone with or without etoposide . (CHOP or EPOCH).
2. Cervix: Paclitaxel with Cisplatin.
4. Lung :Cisplatin with etoposide , cisplatin with gemcitabine.
5. Stomach: Cisplatin with 5-flurouracil.
7. Squamous cell Carcinoma of Buccal mucosa and Conjuctiva : Cisplatin with 5-flurouracil.

Interactions between HAART and Chemotherapy

1. Lamivudine (3TC) - no contraindication
2. Zidovudine (ZDV) - increased risk of anaemia and myelosuppression.
3. Stavudine (d4 T) - possible increased risk of peripheral neuropathy with neurotoxic chemotherapy.
4. Efavirenz (EFV) - no increased risk of toxicity.
5. Nevirapine (NVP) - avoid in individuals receiving hepatotoxic chemotherapy.

### Table 4

<table>
<thead>
<tr>
<th>Anticancer therapy</th>
<th>Primary isoforms that mediate bio-transformation</th>
<th>Interaction with NNRTI drugs (CYP inducers)</th>
<th>Interaction with PI drugs (CYP inhibitors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3A4, 2B6, 2D6</td>
<td>↑</td>
<td>_</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>3A4</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Lomustine</td>
<td>3A4</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>3A4</td>
<td>_</td>
<td>↓</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>3A4</td>
<td>_</td>
<td>↓</td>
</tr>
<tr>
<td>Camptothecins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>3A4</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Topotecan</td>
<td>3A4</td>
<td>↑</td>
<td>_</td>
</tr>
<tr>
<td>Epipophyllotoxins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>3A4</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Taxanes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>3A4</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>3A4, 2C8</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3A4</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Vincristine</strong></td>
<td>3A4</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Kinase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>3A4</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>3A4, 1A2</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
RESULTS

STUDY POPULATION AND PATIENT CHARACTERISTICS

Between August 2009 and July 2010, 36 patients met the eligibility criteria of the proposed study and were recruited. The total number of patients registered in Medical Oncology department during the same period was 2465. Patients with HIV associated Malignancy constituted about 1.46%. The patient characteristics and distribution of malignancy is listed in the Annexure 1.

Table 5 General Profile

<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>1275</td>
<td>1.49</td>
</tr>
<tr>
<td>FEMALE</td>
<td>1190</td>
<td>1.42</td>
</tr>
<tr>
<td>HIV associated cancers</td>
<td>36</td>
<td>1.46</td>
</tr>
<tr>
<td>HIV associated cancers in male</td>
<td>19</td>
<td>52.8</td>
</tr>
<tr>
<td>HIV associated cancers in female</td>
<td>17</td>
<td>47.2</td>
</tr>
</tbody>
</table>

The median age was 39 years (Range 10 years to 60 years). Men comprised 19 out of 36 patients (52.8 %) and women 17 out of 36 patients (47.2 %). AIDS defining malignancies were present in about 47.2% (17 patients) and non–AIDS defining malignancies were seen in about 52.8 % (19 patients).
patients). Men comprised 53% and women 47% in AIDS defining malignancies and the same distribution was seen in non-AIDS defining malignancies also.

**Table 6  Disease Characteristics**

<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS defining Malignancy</td>
<td>17</td>
<td>47.2</td>
</tr>
<tr>
<td>AIDS defining Malignancy in males</td>
<td>9</td>
<td>53</td>
</tr>
<tr>
<td>AIDS defining Malignancy in females</td>
<td>8</td>
<td>47</td>
</tr>
<tr>
<td>Non-AIDS defining Malignancy</td>
<td>19</td>
<td>52.8</td>
</tr>
<tr>
<td>Non-AIDS defining Malignancy in males</td>
<td>10</td>
<td>52.6</td>
</tr>
<tr>
<td>Non-AIDS defining Malignancy in females</td>
<td>9</td>
<td>47.4</td>
</tr>
<tr>
<td>Mean age of AIDS related Malignancy</td>
<td>38 years</td>
<td></td>
</tr>
<tr>
<td>Mean age of non-AIDS related Malignancy</td>
<td>43 years</td>
<td></td>
</tr>
</tbody>
</table>

The median time interval between the diagnosis of HIV and Malignancy was 37 months (Range 6 months to 120 months). It was observed that 25 out of 36 patients (70 %) developed malignancies after a period of time, whereas 11 out of 36 patients (30 %) were diagnosed to have HIV only at the time of diagnosing malignancy. Of these 11 patients, four had AIDS defining
malignancy (36 %) and seven had non-AIDS defining malignancy (67 %). Of the 25 patients with HIV who developed malignancy at a later period, 13 had AIDS defining malignancy (52%) and 12 had non-AIDS defining malignancy (48 %).

All patients except one in this study were adults. The only child was a ten year old female child who had contacted HIV from her mother and had a time interval of 19 months before she presented with HIV defining malignancy of Burkitts lymphoma.

**Table 7 Age Distribution**

<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric AIDS related Malignancy</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>Adult AIDS related Malignancy</td>
<td>35</td>
<td>97.2</td>
</tr>
</tbody>
</table>

All the 11 patients who were diagnosed simultaneously with HIV and Malignancy were started on HAART along with chemotherapy and nine out of 25 (36 %) patients who were diagnosed to have HIV but were not initiated on HAART because of their good CD4 count were also started on HAART along with chemotherapy.
Table 8 HAART Treatment

<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients already on HAART</td>
<td>16</td>
<td>44.5</td>
</tr>
<tr>
<td>Patients started on HAART along with chemotherapy</td>
<td>20</td>
<td>55.5</td>
</tr>
</tbody>
</table>

At the time of beginning the treatment, 23 patients had a Performance status 1 by ECOG (64 %) and 13 patients had a Performance status 2 by ECOG (36 %).

Table 9 Performance Status

<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 1</td>
<td>23</td>
<td>64</td>
</tr>
<tr>
<td>ECOG 2</td>
<td>13</td>
<td>36</td>
</tr>
</tbody>
</table>

Multi-drug resistant Tuberculosis and Hepatitis B infection were present as co-morbidity in three of these patients in this study.
Table 10  Co-morbid Diseases

<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV coexisting AIDS related Malignancy</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>MDR –TB coexisting AIDS related Malignancy</td>
<td>2</td>
<td>5.5</td>
</tr>
</tbody>
</table>

The mean CD4 count at the time of presentation was 234 (Range 59-660). The variation between each cycle of chemotherapy was -37, -40, -19, 0, 0 (Range 33 to -366, 28 to -167, 79 to -150, 32 to -330, 74 to -144 respectively).

Table 11  CD4 Count during treatment

<table>
<thead>
<tr>
<th>Median CD4+ COUNT</th>
<th>234</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variation between successive cycles</td>
<td>74 to -366</td>
</tr>
</tbody>
</table>

Response assessment for all patients showed a complete response (CR) in five patients, partial response (PR) in sixteen patients and death in fifteen patients. The longest follow-up of patient was about 18 months (Range 1-18 months).
Table 12 Response Assessment

<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Partial Response</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>Death</td>
<td>15</td>
<td>42</td>
</tr>
</tbody>
</table>

Follow-up  
Maximum of 18 months (1-18 months)

AIDS Defining Malignancies

In accordance to CDC criteria, only four patients had AIDS defining malignancy. There were two patients with Carcinoma Cervix, one with Burkitts lymphoma and one patient had Plasmablastic variant of DLBCL. AIDS Related Lymphomas were also included in this subgroup of patients. While eleven patients had DLBCL of primarily nodal type, two had extra nodal DLBCL (one in Breast and the other in Buccal mucosa).
<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Types of AIDS defining Malignancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Non-Hodgkins Lymphoma (NHL) – DLBCL</td>
<td>10</td>
<td>28.8</td>
</tr>
<tr>
<td>2. Non-Hodgkins Lymphoma (NHL) – PLASMABLASTIC</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>3. Non-Hodgkins Lymphoma (NHL) – BURKITT'S</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>4. Non-Hodgkins Lymphoma (NHL) – MALT</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>5. Non-Hodgkins Lymphoma (NHL) - DLBCL-BREAST</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>6. Non-Hodgkins Lymphoma (NHL) - DLBCL-BUCCAL MUCOSA</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2. CERVIX</td>
<td>2</td>
<td>5.6</td>
</tr>
</tbody>
</table>

This group had five patients diagnosed with AIDS and Malignancy at presentation. Twelve patients had a time period of 8 to 75 months (median 19 months) from the time of diagnosing HIV to malignancy.

The median initial CD4 count at the first chemotherapy was 220 (range 59-660). The median change in CD4 count with each cycle of chemotherapy
was -38, -41, -20, 0, 0 (range 5 to -120, 20 to -120, 30 to -150, 32 to -50, 8 to -144 respectively).

Response assessment showed two complete responses, five partial responses and eight deaths. Complete response was seen in DLBCL patients, one nodal and the other extra nodal (Buccal mucosa). The patient with nodal DLBCL who had a CR was later found to have re-activation of Hepatitis B virus.

**Table 14 Response in AIDS Defining Malignancies**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>2</td>
</tr>
<tr>
<td>Partial Response</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>10</td>
</tr>
</tbody>
</table>

The follow-up of these patients was up to a maximum of 18 months. Both the patients with CR were on regular follow-up while the patients with partial response had a follow-up of 1, 3, 4, 4, 5 months before they died of malignancy.
NON AIDS DEFINING MALIGNANCY

Non AIDS defining Malignancy was present in 19 patients. The majority presented with Breast cancer (5 patients). Lung, Stomach, Soft Tissue Sarcoma and Conjunctival malignancy were two each, while Myeloma, Hepatocellular carcinoma, Buccal mucosa, Oral cavity, Paranasal sinuses and anal carcinoma were one each.

Table 15  Disease characteristics in non AIDS defining Malignancy

<table>
<thead>
<tr>
<th>Character of cancer patients in the study</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of non- AIDS defining Malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.BREAST</td>
<td>5</td>
<td>14.0</td>
</tr>
<tr>
<td>2.LUNG</td>
<td>2</td>
<td>5.6</td>
</tr>
<tr>
<td>3.STOMACH</td>
<td>2</td>
<td>5.6</td>
</tr>
<tr>
<td>4.MYELOMA</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>5.ANAL CANAL</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>6.SOFT TISSUE SARCOMA</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>7.HEPATOCELLULAR CARCINOMA</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>8.SQUAMOUS CELL CARCINOMA OF ORAL CAVITY</td>
<td>1</td>
<td>2.8</td>
</tr>
</tbody>
</table>
This group had a mean age of 43 years (range 21 – 60 years). Thirteen patients had time interval of 6 to 120 months (median 51 months) from the time of diagnosing HIV to malignancy. This group had six patients diagnosed with AIDS and Malignancy at presentation.

The median initial CD4 count at the first chemotherapy was 345 (range 64-600). The median change in CD4 count with each cycle of chemotherapy was -36, -34, -18, 0, 0 (range 33 to -366, 22 to -167, 79 to -120, 24 to -330, 74 to -40 respectively).

Response assessment showed three complete responses, eleven partial responses and five deaths. Complete response was seen in two patients with Carcinoma Breast and one in Carcinoma of Oral cavity.
Table 16  Response Assessment

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>3</td>
</tr>
<tr>
<td>Partial Response</td>
<td>11</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
</tr>
</tbody>
</table>

The follow-up of these patients was up to a maximum of 15 months. All the three patients with CR were on regular follow-up while three patients with partial response died after 2, 3, 3 months and others are on regular follow-up.

**Acute Toxicity**

Acute toxicities were manageable. The most common toxicity observed was hematological toxicity. Grade 3 toxicities observed were nausea/ vomiting, febrile neutropenia, and hematological toxicity.

A delay in starting subsequent therapy was observed in 14 patients mostly due to febrile neutropenia. The delay was about 7-14 days. Other toxicities were managed symptomatically and patients recovered to proceed on treatment.
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>16</td>
<td>3</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>16</td>
<td>2</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Platelets</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infection,Febreile Neutropenia</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Mucositis</td>
<td>6</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea,Vomiting</td>
<td>3</td>
<td>13</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Renal function</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver function</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
DISCUSSION

Dramatic and prolonged T-cell depletion following the administration of chemotherapy for AIDS-related NHL was described in the pre-HAART era\textsuperscript{103}. There has been a study which has shown that the early recovery of lymphocyte subsets within 3 months of the end of chemotherapy to pre chemotherapy levels and the continued rise of these parameters during prolonged follow-up are reassuring, suggesting that combination chemotherapy with HAART can be safely delivered without long-term immune suppression. This pattern of lymphocyte subset recovery following chemotherapy was similar, although probably swifter than that seen in the immunocompetent population\textsuperscript{104}.

This study has been devised to assess the effect of chemotherapy on immunological parameters (CD4+) in patients with malignancy on HAART. Our results show that there is a variation in CD4 count during chemotherapy and HAART in both AIDS defining Cancers (ADC) and Non AIDS defining Cancers (nADC). This has also been documented during chemotherapy in other studies. The change in CD4 cell count from the start to end of chemotherapy variation in our study was 74 to \(-366\). The same observation is found in other studies\textsuperscript{58, 60, 62, 84}. The immunological recovery after completion of treatment was also studied by the above investigators and they have found that in patients who survive, CD4 count improves and reaches the pre-chemotherapy status by the third month.
Whether the change in CD4 count correlated with survival is the question to be answered. In our study, of the five patients who achieved complete response, four patients had sustained CD4 count while the fifth patient had decreasing CD4 count with a nadir of 99 at the beginning of sixth cycle of chemotherapy. In patients with partial response, all patients had a CD4 count which did not vary much with each cycle of chemotherapy. This leads to the group of patients who died during chemotherapy, whose CD4 count analysis did show that there was a persistent low CD4 count throughout the treatment period.

The response rates also reveal an interesting observation. The patients who presented with a poor performance status, advanced disease and an initial low CD4 count had Grade III febrile neutropenia at the end of first cycle itself and this lead to delay in subsequent chemotherapy. This was also the group who died during treatment.

AIDS related lymphoma (ARL) was the commonest cancer in our study. AIDS related Lymphomas (ARL) has been observed to have a better prognosis with the advent of HAART\textsuperscript{57-66}. All these patients had advanced stage, B symptoms, extranodal involvement such as bone marrow and central nervous system at the time of presentation. Mortality in AIDS-associated cancers was higher when these patients had low CD4 count and Karnofsky performance score, presence of extranodal disease, an advanced clinical stage, presence of bone marrow involvement, an age more than 35 years and a high serum lactate
dehydrogenase. In our study, we found that ARL had a 50% death rate (8 out of 15). This observation can be attributed to the above said reasons and also the presence of MDR-TB in two of those patients. This is in line with the fact that the biology of the primary tumor plays a major role in response\textsuperscript{105}. An interesting fact is that there was no patient with Primary CNS Lymphoma, Primary Effusion Lymphoma or Kaposi’s Sarcoma in our study which is in contrast to that as seen in Western countries, where the incidence is high.

Our results show that there is an increase in Non AIDS defining Cancer (nADC). Though Cervical Cancer is a common malignancy in India, we had only two patients in this study. This is attributed to the Personian bias of referring Carcinoma Cervix to the Women and Children’s Hospital. A notable subset was Squamous Cell Carcinoma of the Conjunctiva, which is on an increasing trend. Among nADC, Hodgkins Lymphoma, has been observed to be increasing in incidence in Western countries due to prolonged survival of AIDS patient on HAART (subsequent to increased T cell milieu caused by HAART). In our study there was no Hodgkins Lymphoma even though there were 16 patients already taking HAART.

The other method to study the impact of chemotherapy on the immunological parameter of HIV infection is to quantify the viral load. The studies which have studied the CD4 cell dynamics and chemotherapy had also studied the viral load. The trials found a significant decrease during chemotherapy of $-1.61 \log_{10}$ copies/mL and $-2 \log_{10}$ copies/mL and -
2.8\log_{10} \text{copies/mL} \text{ during chemotherapy with HAART.} \text{ The study describing the maximal responses reports a decline in median HIV viral load from 29 000 copies/mL at the start of chemotherapy to less than 500 copies/mL. In contrast, DA-EPOCH therapy without concomitant HAART was associated with a median rise in viral load during chemotherapy of } +0.83 \log_{10} \text{ copies/mL.} \text{ (62). NACO’s operational guidelines does not allow for measurement of viral load except in a scenario where the patient becomes refractory to HAART.}

Another focus of this study was to examine the acute toxicities of the treatment. All patients on HAART were initiated with tablet Septran (Sulfamethoxazole /trimethoprim ) as a prophylactic measure. Immune Reconstitution Inflammatory Syndrome ( IRIS ) observed in patients after starting on HAART was not observed in our study. Grade III hematological toxicities observed and life threatening was febrile neutropenia . Other toxicities observed were manageable with good supportive care.

This analysis confirms that chemotherapy and concomitant HAART for AIDS-related Malignancies do not cause prolonged suppression of lymphocyte subsets.
CONCLUSION

In conclusion, we have identified that

1) The surrogate parameter to assess the immune competence of HIV patients is CD4 count, which is found to be varying with each cycle of chemotherapy

2) The final response outcome depends on the initial CD4 count, change in CD4 count between chemotherapy cycles, performance status of the patient, pathobiology and aggressiveness of the malignancy and opportunistic infection.

3) Concurrent chemotherapy and HAART has been observed to be feasible in our study.

4) Non AIDS defining Malignancies are increasing in incidence which can be attributed to the increased life expectancy with HAART.
Non AIDS Defining Malignancies

Sex Analysis

Type of Diseases

- BREAST
- MYELOMA
- LUNG
- STOMACH
- SCC CONJ
- SCC BM
- HCC
- STS
- ANAL
- SCC OC
Response Assessment

Change in CD 4 count
AIDS DEFINING MALIGNANCIES

Sex Analysis

Type of Diseases

- NHL
- NHL-BRST
- NHL-BM
- CERVIX

Sex Analysis:
- M: 9
- F: 8

Type of Diseases:
- NHL: 13
- NHL-BRST: 2
- NHL-BM: 1
- CERVIX: 1

Sex Analysis:
- M: 9
- F: 8

Type of Diseases:
- NHL: 13
- NHL-BRST: 2
- NHL-BM: 1
- CERVIX: 1
Response Assessment

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Number of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>10</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>5</td>
</tr>
</tbody>
</table>

VARIATION BETWEEN SUCCESSIVE CYCLES

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Cycle 1-2</th>
<th>Cycle 2-3</th>
<th>Cycle 3-4</th>
<th>Cycle 4-5</th>
<th>Cycle 5-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
General Profile

Sex Analysis

Disease Characteristics
Response Assessment

Variation in CD 4 count between chemotherapy cycles
BIBLIOGRAPHY

1. Steinbrook R HIV in INDIA- A Downsized Epidemic NEJM 2008;358;107-109


15. CDC. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. Morbidity and Mortality Weekly Report 1987;36:1S–15S.


33. MMWR 42(No. RR-17), December 18, 1992


83. Sparano J, Lee J, Kaplan L. Randomized phase II trial of infusional EPOCH chemotherapy given either concurrently with or sequentially followed by rituximab in HIV-associated


