Immunological recovery in survivors following chemotherapy for AIDS related non Hodgkin's lymphoma

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Running title: Late toxicity in ARL

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Abstract

Purpose
Late effects of chemotherapy on immunological parameters in AIDS-related NHL have not been described.

Patients and Methods
From a cohort of 105 consecutive patients treated with infusional chemotherapy and HAART, 68 survived more than 3 months following the end of chemotherapy. Their lymphocyte subsets and plasma HIV viral loads were measured at regular intervals for 2 years and values compared to baseline.

Results
During chemotherapy, there were statistically significant falls in CD4 (helper T), CD8 (cytotoxic T) and CD19 (B) cell populations but no changes in the CD56 (natural killer) cell population. Amongst the 68 survivors, there were statistically significant increases in CD4, CD8, CD19 and CD56 cell populations during the first year of follow-up, compared to the values at the start of chemotherapy. During the second year of follow up there were further statistically significant rises in CD4 and CD19 cell populations, compared to the values at 12 months post chemotherapy. During 244 years of follow-up following chemotherapy in these 68 survivors, 7 second primary tumours and 8 opportunistic infections were diagnosed.

Conclusion
Chemotherapy and concomitant HAART for AIDS-related NHL does not cause prolonged suppression of lymphocyte subsets. These data should provide reassurance regarding the long term consequences of chemotherapy in these individuals.

Keywords
AIDS, HIV, NHL, HAART, Chemotherapy, Lymphocyte subsets.
Introduction

The last decade has shown dramatic improvements in the management of AIDS related non-Hodgkin’s lymphoma (NHL). Studies from the post HAART era report response rates and short-term survival rates approaching those in immunocompetent patients1-8. A new prognostic index for AIDS related NHL confirms this, and demonstrates that the international prognostic index (IPI), which was established for aggressive NHL in the immunocompetent population, is also a valuable predictor of survival in AIDS related NHL, especially when combined with CD4 cell count at the time of lymphoma diagnosis9. Despite these encouraging results, malignancies including lymphoma are emerging as one of the major causes of death in patients with HIV who have access to HAART10,11.

Most published series describe the outcome of treatment of AIDS related NHL with relatively short follow-up and there remain concerns over the late effects of chemotherapy in people with AIDS especially the late effects on immunological parameters. Indeed studies in the pre-HAART era suggested persistent severe immunosuppression following chemotherapy for AIDS related NHL12. These worries remain and were highlighted by the results of AIDS-malignancies consortium trial 010, comparing CHOP and R-CHOP in 149 patients with AIDS related NHL13. This study revealed an excess of deaths due to infection after completion of chemotherapy especially amongst patients with very low CD4 cell counts (< 50 cells/mL) enrolled to receive R-CHOP with maintenance rituximab whose lymphoma was in remission. We do not however know whether these complications were therapy-related or whether they were due to prior advanced immunosuppression.

We have previously reported that treatment with concomitant HAART and chemotherapy for AIDS related lymphoma resulted in lymphocyte subset suppression during chemotherapy and suggested early restoration of CD4 cell counts after completing chemotherapy14. We sought to assess the late immunological impact of chemotherapy on a cohort of patients successfully treated for AIDS related NHL.

Methods

Patients

All patients diagnosed with HIV related high grade NHL at our institution between 1999 and 2006 were treated with a combination of infusional CDE (cyclophosphamide, doxorubicin and etoposide) chemotherapy15 and HAART (highly active antiretroviral therapy) comprising a combination of at least three antiretroviral agents including a nucleoside analogue backbone combined with a protease inhibitor and or a non-nucleoside reverse transcriptase inhibitor. All patients had histologically confirmed aggressive high grade NHL and full staging at diagnosis. The immunologic analysis here focuses on individuals surviving for more than 3 months after completing the course of chemotherapy and this study was approved by the Chelsea and Westminster
institutional review board. Informed consent was provided in accordance with the Declaration of Helsinki.

Follow-up and immune subsets

Following completion of chemotherapy, patients were seen at least once a month for the first year and thereafter at least once every 3 months. Lymphocyte subsets and plasma HIV-1 viral load were measured at the start of chemotherapy, after 1 and 3 months on chemotherapy, at the completion of chemotherapy, 1 month after completing chemotherapy and thereafter at 3, 6, 12, 18 and 24 months after chemotherapy. Opportunistic infection prophylaxis was stopped following chemotherapy when the CD4 cell count achieved appropriate levels, whilst all patients continued on their HAART.

Total lymphocyte and subset analysis was performed using whole blood stained with murine anti-human monoclonal antibodies to CD4 (T helper cells), CD8 (a cytotoxic T cell marker), CD19 (B cells) and CD16/56 (natural killer cells) (TetraOne, Beckman Coulter®, High Wycombe, UK) and were evaluated on an Epics XL-MCL (Beckman Coulter®) multiparametric four colour flow cytometer. Plasma viral loads (Quantiplex HIV RNA 3.0, Chiron, Halstead, UK) were recorded with a lower limit of detection of 50 copies/mL.

Statistical methods

Median and interquartile ranges for lymphocyte subsets are described and the variation of lymphocyte subsets in subjects over time are analysed by paired t-test statistics. We used Mann Whitney U test to compare non-parametric variables between groups.

Results

Patient characteristics

Between January 1999 and December 2006, 105 patients with high grade HIV associated NHL were treated with CDE chemotherapy and HAART. The characteristics at presentation of the entire cohort and the study group of 68 survivors are shown in Table 1. As expected, the survivors had statistically significantly lower risk IPI scores whether measured as composite IPI risk groups or individual variables (ECOG performance score, stage, elevated serum LDH, although not number of extranodal sites). In addition CD4 cell count at NHL diagnosis was significantly higher in the survivors.

Survival data

Overall, 42 patients have died and 63 survive at a median follow-up of 3.8 years and the 5 year overall survival is 59% (95%CI: 49 to 68%). Twenty two patients died during the planned cycles of chemotherapy, 14 from progressive lymphoma, 7 from sepsis (4 during their first two cycles of chemotherapy) and 1 from a cerebrovascular accident. Seventeen patients have died of recurrent
lymphoma including 8 with leptomeningeal disease recurrence. Three patients have died whilst in remission of lymphoma; the causes of these deaths are: 1 gastric cancer second primary malignancy, 1 esophageal cancer second primary malignancy and 1 cardiac event.

Immunological effects during chemotherapy

During the course of chemotherapy and one and three months following completion of the chemotherapy, patients had lymphocyte subsets measured and HIV plasma viral loads. From the initial cohort of 105 patients, 68 survived to the 3 months post chemotherapy time point, thus the number of subjects at each time point diminishes and this may confound interpretation of results. During the chemotherapy there were statistically significant declines in the CD4 (helper T cell), CD8 (cytotoxic T cell) and CD19 (B cell) cell populations in the peripheral blood but no significant change in the CD56 (natural killer cell) population (see Table 2). At diagnosis of lymphoma, 62/105 (59%) of the patients were on HAART and the remaining patients all started HAART with their chemotherapy. At the start of chemotherapy only 27% patients had an undetectable HIV plasma viral load. This value rose steadily through the course of chemotherapy to 69% at the completion of chemotherapy and on to 79% 3 months after completing chemotherapy. This rise in the proportion of patients with undetectable viral loads will mainly be because 41% of the cohort were antiretroviral naïve and started HAART with their chemotherapy.

Late immunological effects following chemotherapy

Lymphocyte subset and plasma HIV viral load data are available for 68 patients 3 months after completing chemotherapy and further measurements of these factors has been undertaken at 6 (n=64), 12 (n=54), 18 (n=47) and 24 (n=43) months after completing chemotherapy. For the analysis of late immunological toxicity amongst these survivors, only these 68 patients are included in order to eradicate any bias. During the first year of follow-up from the end of chemotherapy, there were statistically significant rises in CD4, CD8, CD19 and CD56 cell counts and the undetectable rate rose from 69% to 81%. The rises in cell counts were most marked during the first 3 months of follow-up, and the median rise in cell counts over the first year were 97 cells/mL for CD4, 318 cells/mL for CD8, 137 cells/mL for CD19 and 32 cells/mL for CD56. During the second year of follow-up further statistically significant rises were documented for CD4 and CD19 cell counts but not for CD8 or CD56 cell counts (see table 3 and figure 1). Data are available for 43 patients at 24 months post chemotherapy and for these patients the CD4 cell count rose from 165/mL (IQR: 62-252) at the start of chemotherapy to 270/mL (IQR: 174-445) 24 months after completing chemotherapy.

Delayed toxicity following chemotherapy

Sixty eight patients were monitored during late follow-up (more than 3 months after completing chemotherapy). The total follow-up for these patients is 244 patient years. Seven patients developed second primary tumors (2 Kaposi sarcoma, 1 each anal squamous cancer, esophageal cancer, renal cell cancer, skin basal cell cancer and skin squamous cell cancer) and a further 3
patients developed cervical intraepithelial neoplasia (CIN). During this period of follow-up 7 patients developed 8 AIDS defining opportunistic infections: 3 non-pulmonary TB, 1 each cerebral toxoplasmosis, cryptosporidiosis, visceral leishmaniasis, pneumocystis carinii pneumonia and esophageal candidiasis (last two diagnoses in the same individual).

Discussion

Dramatic and prolonged T cell depletion following the administration of chemotherapy for AIDS related NHL was described in the pre-HAART era. We describe the use of infusional CDE chemotherapy with HAART in 105 patients with AIDS associated aggressive high grade NHL and the early and delayed immunological sequelae of this treatment. 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 is reassuring suggesting that combination chemotherapy with HAART can be safely delivered without long-term immune suppression. This pattern of lymphocyte subset recovery following chemotherapy is similar, although probably swifter than that seen in the immunocompetent population. Moreover, during a median follow-up of 3.8 years there were relatively few AIDS defining opportunistic infections.

We have previously described the depression of CD4 and CD19 cells during chemotherapy and HAART treatment in both lymphoma (including 10 patients who are also included in this study) and Kaposi’s sarcoma. This has also been documented during chemotherapy in other studies, however the findings are often complicated by the initiation of HAART with the chemotherapy in antiretroviral naïve patients, whilst patients already on HAART continue with it. Moreover none of the reports compare the pre and post chemotherapy lymphocyte subsets and HIV viral loads in the survivors and so all these analyses are biased by patients who fail to complete therapy. Five studies have reported changes in CD4 cell counts during chemotherapy including 4 where patients received concomitant HAART. In three manuscripts the fall in CD4 cell count from the start to end of chemotherapy is described in 361, 103 and 203 patients with declines in median or mean CD4 cell counts recorded of -47 cells/mL, -106 cells/mL and -61 cells/mL respectively. One paper describes a median rise in CD4 cell count from the start of chemotherapy to its maximal value of +216 cells/mL although it is not clear when the maximum CD4 cell count was recorded in relationship to the chemotherapy. The fifth manuscript describes therapy with the dose adjusted DA-EPOCH chemotherapy regimen used at the NCI that requires the interruption of HAART for the entire duration of chemotherapy. During DA-EPOCH chemotherapy, the CD4 count fell by a median of 189 cells/mm³ by the end of chemotherapy.

With regard to HIV viral load, the first three trials found a significant decrease during chemotherapy of -1.61 log₁₀ copies/mL and -2 log₁₀ copies/mL and -2.8 log₁₀ copies/mL during chemotherapy with HAART. The study describing the
maximal responses at uncertain timing reports a decline in median HIV viral load from 29,000 copies/mL at the start of chemotherapy to <500 copies/mL\(^4\). In contrast DA-EPOCH therapy without concomitant HAART was associated with a median rise in viral load during chemotherapy of +0.83 log\(_{10}\) copies/mL\(^1\). A further paper describes the maintenance of virological response during the administration of both R-CDE and CHOP chemotherapy finding 68% and 84% respectively of patients maintained a virological response while receiving chemotherapy\(^2\). In this study, HIV genotype and virtual phenotype analysis was carried out on patients who suffered virological failure and the authors concluded that chemotherapy does not significantly increase the occurrence of new HIV resistance patterns\(^2\).

In three previous reports some information is available on recovery times of lymphocyte subsets and virological control following completion of chemotherapy. Again these results do not control for patients who do not survive the chemotherapy. Antinori et al\(^1\) report that the median C4 cell count 6 months post chemotherapy was +25 cells/mL higher than at the start of chemotherapy and at 9 months was 178 cells/mL higher than at the end of chemotherapy. In our previous small study of 20 patients, the median CD4 cell count was 49 cells/mL higher 3 months after completing chemotherapy than at the start of chemotherapy\(^1\). In contrast with the DA-EPOCH regimen HAART is recommenced at the completion of chemotherapy and the CD4+ cells took 6-12 months to recovery to baseline values\(^1\). HIV viral load dropped by 2.8 log\(_{10}\) copies/ml at 6 months post chemotherapy in one study\(^1\) and 2.6 log\(_{10}\) copies/ml at 3 months in another\(^1\). With DA-EPOCH, at 3 months post chemotherapy the viral load had fallen a median of 0.61 log\(_{10}\) copies/ml compared to baseline levels\(^1\). These three studies reporting recovery after chemotherapy however do not compensate for survival and compare the values for all patients starting chemotherapy with the values following chemotherapy only of the survivors. This study compensates for bias by describing the lymphocyte subsets after completion of chemotherapy separately in the 67 patients who survived more than 3 months after the end of chemotherapy and in this study the follow up of 3.8 years is appreciably longer than in previous published reports.

One potential short-coming of the analysis of delayed immunological effects in this cohort is that inevitably only those patients who survived lymphoma can be studied. Thus the rapid immune cell recovery following chemotherapy may reflect favourable outcome and it is possible that under these circumstances the immune cells may be contributing an anti-lymphoma effect. These data present evidence that in those individuals who survive lymphoma, the immune subsets with the strongest mechanistic anti-tumor data (NK and CD8 cells) are maintained, although we have not measured specific anti-tumor CTLs.

The delayed follow-up for the 68 patients who survived at least 3 months after completing chemotherapy is 244 patient years. During this follow-up, 7 developed second primary tumors. The development of Kaposi’s sarcoma in 2
patients may relate to the chemotherapy induced lymphocyte suppression as CD4 cell nadir, CD8 cell nadir, B cell nadir but not natural killer cell nadir correlate with the risk of developing KS. The 5 non AIDS defining cancers observed in this study follow-up period have been shown to occur at increased frequency in people with HIV although a direct correlation with immunological parameters has not been established.

This analysis confirms that chemotherapy and concomitant HAART for AIDS related NHL does not cause prolonged suppression of lymphocyte subsets and will alleviate clinicians’ fears that this treatment may compromise long-term immunological function in people with AIDS.

Author contributions: All authors contributed to the long term follow up and patient care of this large cohort and analyzed and provided data. MB, BG, TP and MN were the clinicians in overall charge and all authors conceptualised and approved the study. TP, JS and MB wrote the final paper which was reviewed by all the authors. The authors declare no competing financial interests.
References


Table 1. Patient characteristics at lymphoma presentation of entire cohort and comparison with study group who survived > 3months after chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Survivors (&gt;3month post chemo)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>105</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>92/105 (88%)</td>
<td>61/68 (90%)</td>
<td>$\chi^2$ p=0.38</td>
</tr>
<tr>
<td><strong>Median age (range)</strong></td>
<td>43 (22 to 77)</td>
<td>41 (22 to 68)</td>
<td>MW U test p=0.33</td>
</tr>
<tr>
<td><strong>Prior AIDS defining illness</strong></td>
<td>13/105 (12%)</td>
<td>9/68 (13%)</td>
<td>$\chi^2$ p=0.71</td>
</tr>
<tr>
<td><strong>Median CD4 (range)</strong></td>
<td>162 (2 to 814)</td>
<td>178 (8 to 636)</td>
<td>MW U test p=0.042</td>
</tr>
<tr>
<td><strong>On HAART at NHL diagnosis</strong></td>
<td>62/105 (59%)</td>
<td>40/68 (59%)</td>
<td>$\chi^2$ p=0.95</td>
</tr>
<tr>
<td><strong>Undetectable plasma HIV viral load at diagnosis</strong></td>
<td>28/105 (27%)</td>
<td>21/68 (31%)</td>
<td>$\chi^2$ p=0.19</td>
</tr>
<tr>
<td><strong>Stage III/IV</strong></td>
<td>87/105 (83%)</td>
<td>53/68 (78%)</td>
<td>$\chi^2$ p=0.07</td>
</tr>
<tr>
<td><strong>&gt;1 extranodal site</strong></td>
<td>52/105 (49%)</td>
<td>29/68 (43%)</td>
<td>$\chi^2$ p=0.056</td>
</tr>
<tr>
<td><strong>LDH raised</strong></td>
<td>72/105 (69%)</td>
<td>41/68 (60%)</td>
<td>$\chi^2$ p=0.013</td>
</tr>
<tr>
<td><strong>IPI:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>22 (21%)</td>
<td>19 (28%)</td>
<td>$\chi^2$ p=0.0016 for IPI groups</td>
</tr>
<tr>
<td><strong>Low Intermediate</strong></td>
<td>26 (25%)</td>
<td>20 (29%)</td>
<td></td>
</tr>
<tr>
<td><strong>High Intermediate</strong></td>
<td>30 (29%)</td>
<td>19 (28%)</td>
<td></td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>27 (26%)</td>
<td>10 (15%)</td>
<td></td>
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</tbody>
</table>

IPI = International prognostic index  
MW U = Mann Witney U test
Table 2. Changes in HIV plasma viral load and lymphocyte subsets during and shortly after CDE chemotherapy (chemo) for entire cohort of 105 patients. IQR = interquartile range. All p values were calculated by paired t-tests.

<table>
<thead>
<tr>
<th></th>
<th>Median value at start of chemo (IQR)</th>
<th>Median change from baseline at 1m on chemo (IQR)</th>
<th>Median change from baseline at 3m on chemo (IQR)</th>
<th>Median change from baseline at end of chemo (IQR)</th>
<th>Median change from baseline at 1m post chemo (IQR)</th>
<th>Median change from baseline at 3m post chemo (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>105</td>
<td>97</td>
<td>88</td>
<td>81</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>162/mL (66 to 269)</td>
<td>-15 (-75 to +36) p=0.16</td>
<td>-29 (-95 to +33) p=0.0055</td>
<td>-41 (-129 to +16) p&lt;0.0001</td>
<td>-30 (-77 to +45) p=0.18</td>
<td>+14 (-59 to +72) p=0.59</td>
</tr>
<tr>
<td>CD8 cell count</td>
<td>664/mL (462 to 984)</td>
<td>-120 (-367 to +71) p&lt;0.0001</td>
<td>-294 (-567 to +42) p&lt;0.0001</td>
<td>-308 (-589 to +20) p=0.0001</td>
<td>-84 (-422 to +142) p=0.054</td>
<td>+88 (-279 to +364) p=0.64</td>
</tr>
<tr>
<td>CD19 cell count</td>
<td>86/mL (47 to 170)</td>
<td>-63 (-144 to -18) p&lt;0.0001</td>
<td>-75 (-165 to -39) p&lt;0.0001</td>
<td>-80 (-168 to -42) p&lt;0.0001</td>
<td>-69 (-138 to -20) p&lt;0.0001</td>
<td>-8 (-62 to +29) p=0.14</td>
</tr>
<tr>
<td>CD56 cell count</td>
<td>59/mL (29 to 116)</td>
<td>-6 (-34 to +15) p=0.49</td>
<td>-2 (-44 to +22) p=0.12</td>
<td>-10 (-44 to +28) p=0.059</td>
<td>+5 (-25 to +27) p=0.41</td>
<td>+7 (-22 to +29) p=0.97</td>
</tr>
<tr>
<td>Percentage HIV VL &lt;50 copies/ml</td>
<td>27%</td>
<td>36%</td>
<td>57%</td>
<td>69%</td>
<td>74%</td>
<td>79%</td>
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Table 3. Changes in HIV plasma viral load and lymphocyte subsets after chemotherapy for study group of 68 patients who survived > 3months after completing chemotherapy (chemo).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Median value at start of chemo (IQR)</th>
<th>Median value at end of chemo (IQR)</th>
<th>Median change from end of chemo at 1m post chemo (IQR)</th>
<th>Median change from end of chemo at 3m post chemo (IQR)</th>
<th>Median change from end of chemo at 6m post chemo (IQR)</th>
<th>Median change from end of chemo at 12m post chemo (IQR)</th>
<th>Median change from end of chemo at 18m post chemo (IQR)</th>
<th>Median change from end of chemo at 24m post chemo (IQR)</th>
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<tr>
<td><strong>First year following chemo</strong></td>
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<tr>
<td>Subjects</td>
<td>68</td>
<td>68</td>
<td>68</td>
<td>68</td>
<td>64</td>
<td>54</td>
<td>47</td>
<td>43</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>178/mL (66 to 269)</td>
<td>127/mL (66 to 269)</td>
<td>+15.5 (-8.5 to 97) p=0.0008</td>
<td>+47 (+13 to 122) p&lt;0.0001</td>
<td>+69 (+14 to 134) p&lt;0.0001</td>
<td>+97 (+54 to 193) p&lt;0.0001</td>
<td>+33 (-27 to 193) p=0.030</td>
<td>+48 (+3 to 128) p=0.0003</td>
</tr>
<tr>
<td>CD8 cell count</td>
<td>693/mL (462 to 984)</td>
<td>440/mL (66 to 269)</td>
<td>+130 (-30 to 404) p&lt;0.0001</td>
<td>+279 (+77 to 565) p&lt;0.0001</td>
<td>+243 (+77 to 1446) p&lt;0.0001</td>
<td>+318 (+110 to 562) p&lt;0.0001</td>
<td>-21 (-188 to 221) p=0.85</td>
<td>+14 (-160 to 244) p=0.32</td>
</tr>
<tr>
<td>CD19 cell count</td>
<td>95/mL (47 to 170)</td>
<td>3/mL (66 to 269)</td>
<td>+3.5 (0 to 33) p&lt;0.0001</td>
<td>+80 (+38 to 126) p&lt;0.0001</td>
<td>+102 (+56 to 155) p&lt;0.0001</td>
<td>+137 (+85 to 256) p&lt;0.0001</td>
<td>+10 (-32 to 66) p=0.055</td>
<td>+34 (-11 to 93) p=0.0036</td>
</tr>
<tr>
<td>CD56 cell count</td>
<td>59/mL (29 to 116)</td>
<td>43/mL (66 to 269)</td>
<td>+4 (-6 to 33) p=0.066</td>
<td>+7 (-8 to +39) p=0.005</td>
<td>+15 (-8 to +60) p&lt;0.0001</td>
<td>+32 (-3 to +89) p&lt;0.0001</td>
<td>-4 (-25 to 28) p=0.94</td>
<td>+12 (-36 to +4) p=0.89</td>
</tr>
<tr>
<td><strong>Second year following chemo</strong></td>
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<tr>
<td>Subjects</td>
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<td>68</td>
<td>64</td>
<td>54</td>
<td>47</td>
<td>43</td>
</tr>
<tr>
<td>Start chemo</td>
<td>End chemo</td>
<td>1m post chemo</td>
<td>3m post chemo</td>
<td>6m post chemo</td>
<td>12m post chemo</td>
<td>18m post chemo</td>
<td>24m post chemo</td>
<td></td>
</tr>
<tr>
<td>Percentage HIV VL &lt;50 copies/ml</td>
<td>31%</td>
<td>69%</td>
<td>75%</td>
<td>79%</td>
<td>81%</td>
<td>87%</td>
<td>87%</td>
<td>90%</td>
</tr>
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</table>
Figure 1. Graph of median lymphocyte subset cell counts during and following chemotherapy for 68 patients who survived >3 months after completing chemotherapy.
Immunological recovery in survivors following chemotherapy for AIDS related non Hodgkin’s lymphoma

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