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Combination antiretroviral therapy accelerates immune recovery in patients with HIV-related lymphoma treated with EPOCH: a comparison within one prospective trial AMC034

Carlyn Rose C. Tan¹, Stefan K. Barta¹, Jeannette Lee², Michelle A. Rudek³, Joseph A. Sparano⁴, and Ariela Noy⁵

¹Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA

²Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

³Department of Oncology, School of Medicine, Johns Hopkins University, Baltimore, MD, USA

⁴Department of Oncology, Montefiore-Einstein Cancer Center, Montefiore Medical Center, Bronx, NY, USA

⁵Department of Medicine, Memorial Sloan-Kettering Cancer Center/Weill-Cornell Medical College, New York, NY, USA

Abstract

Drug-drug interactions between cART and chemotherapy may impact HIV and lymphoma control or lead to increased toxicities. No prospective comparative data informs potential harms and benefits. In AMC034 HIV-associated high-grade B-cell NHL patients received DA-EPOCH with rituximab. cART was given with EPOCH or delayed until chemotherapy completion per investigator choice. Pharmacokinetic, immunological and treatment effects of concurrent cART were evaluated. CD4 counts dropped during EPOCH in both groups but recovered to higher than baseline 6 months post-EPOCH only in the cART group. HIV viral load decreased during chemotherapy in the cART group but increased in the non-cART group. Incidence of grade 3 infectious, hematologic, or neurological toxicities was similar. Concurrent cART was not associated with 1-year EFS or OS. cART with EPOCH was well-tolerated and allowed for faster immune recovery. While we did not observe differences in outcome, the preponderance of evidence is in favor of combining cART with chemotherapy.

This study is registered at <http://clinicaltrials.gov> as NCT00049036.

Keywords

HIV-associated lymphoma; combination antiretroviral therapy; chemotherapy; dose-adjusted EPOCH; HIV; AIDS

Introduction

Despite the introduction of cART, the incidence of non-Hodgkin lymphoma (NHL) remains significantly increased in HIV-positive individuals compared to the HIV-negative population. (1–3) In the pre-cART era, treatment of HIV-associated NHL was mainly palliative with low-dose chemotherapy.(4) The median survival was measured in months with approximately 10% of patients alive at two years.(5)

Introduced in 1996, cART dramatically altered management and improved prognosis of patients with HIV-associated NHL by reducing morbidity and mortality from HIV infection and allowing for more aggressive lymphoma-directed therapy.(6–8) People living with HIV (PLWH) are now able to tolerate highly aggressive and potentially curative treatments and achieve outcomes similar to those of immunocompetent patients with *de novo* NHL without prohibitive toxicity.(9–12)

Due to a lack of prospective comparative data, controversy exists regarding the concomitant use of cART during lymphoma treatment. Arguments that cART should be suspended during treatment include concerns of additive depletion of hematopoietic reserve, potential overlapping toxicities, drug-drug interactions, as well as potential problems with cART adherence due to chemotherapy-related toxicities.(13, 14) In contrast, administration of cART with chemotherapy is based on concerns of uncontrolled HIV replication during cART cessation, which may further weaken immune function. A meta-analysis of 1,546 patients from 19 trials with HIV-associated NHL demonstrated that concurrent cART and chemotherapy was associated with statistically improved complete response (CR) rates with a trend toward improved overall survival (OS).(15) Nevertheless, no study compares the effects of cART administered or held during chemotherapy within the same prospective clinical trial. Therefore, we analyzed clinical data from the AIDS Malignancy Consortium 034 (AMC034) trial to evaluate the effect of concurrent cART on immune function, drug interactions, and treatment outcomes during dose-adjusted EPOCH (DA-EPOCH) plus concurrent or sequential rituximab.

Methods

Patients and AMC034 Trial Design

AMC034 enrolled HIV-positive adults with untreated aggressive CD20-positive B-cell NHL (diffuse large B-cell lymphoma, high-grade large cell immunoblastic lymphoma, anaplastic large cell lymphoma, Burkitt lymphoma, high-grade B-cell lymphoma and Burkitt-like lymphoma) with adequate performance status (ECOG 0–2) and organ function. Patients with primary CNS lymphoma, lymphomatous meningitis, active HIV-associated opportunistic infections (OI), or concurrent malignancies were excluded.

In this “pick-the-winner” phase II trial patients were randomized in a 1:1 fashion to receive DA-EPOCH (infusional etoposide, doxorubicin, and vincristine, bolus cyclophosphamide, and oral prednisone) plus concurrent rituximab given with each cycle (DA-EPOCH-R) or sequential rituximab given every three weeks for six cycles beginning four weeks after

completing EPOCH (DA-EPOCH→R). The cyclophosphamide dose was adjusted for cycles 2–6 based on nadir absolute neutrophil and platelet counts as previously described.(16)

Whether cART was used with EPOCH was left to investigator discretion. It was recommended to keep patients on cART if they were on a stable regimen prior to the lymphoma diagnosis and to withhold cART for antiretroviral-naïve patients until after completion of EPOCH. Despite this, some patients initiated cART after cycle one or two. For our analysis, patients were considered to be on concurrent cART if therapy was initiated no later than by cycle two of EPOCH though pharmacokinetic analysis was based on whether the patient was on cART at the time of pharmacokinetic sampling. Of note, zidovudine was prohibited during chemotherapy due to known myelosuppression.

The study was approved by the Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) and by the local institutional review board of each participating institution.

Measurements of HIV viral load, CD4 and CD8 counts

T-cell subsets and HIV RNA PCR were measured pre-treatment during screening, at the end of cycle two of EPOCH, then one, three, and six months after completion of EPOCH. Measurements were performed at local laboratories of the study sites as per their respective institutional protocols.

Pharmacokinetics

Samples were collected at 3 time points (i.e., 24–48, 48–72, and 72–96 hours) after the start of the first infusion. Doxorubicin, etoposide, and vincristine levels were analyzed by HPLC. Steady-state concentrations were the average of the 3 time points. The clearance was derived by dividing the drug-infusion rate by the steady-state concentrations. Clearance was summarized using descriptive statistics according to the ability of cART to induce or inhibit CYP3A4, a cytochrome P450 enzyme involved in the metabolism of doxorubicin,(17, 18) etoposide,(19, 20) and vincristine.(21, 22) In this case, patients were stratified into groups based on the known drug-drug interaction potential into 4 categories: residual/concurrent CYP3A4 inhibition, residual/concurrent CYP3A4 induction, residual/concurrent CYP3A4 inhibition and induction (on a regimen with both an inducer and an inhibitor), and no interaction potential or not on cART.

Statistical analysis

Summary statistics were used to describe patient characteristics. HIV viral load (VL) was analyzed as a continuous variable; undetectable levels and those <50 copies/μL were defined as zero. Cyclophosphamide dose-intensity was defined as mean dose per cycle.

The Wilcoxon rank sum test was used to compare the two antiretroviral groups with respect to baseline levels of HIV VL, CD4 and CD8 counts, number of cycles and cyclophosphamide dose. Generalized estimating equations (GEE) were used to evaluate the effects of treatment arm, and cycle with changes in the HIV VL, and CD4 and CD8 counts (using the log10 transformation) adjusting for inpatient variation for each group. Logistic

regression was used to evaluate the effects of cART and treatment arm on overall response (OR) and CR rate. The log-rank test and proportional hazards model were used to evaluate the effect of cART on OS and event-free survival (EFS). Fisher's exact test and the logistic regression model were used to evaluate the role of cART on grade 3 or 4 hematologic, infectious, and neurologic toxicities (CTCAE v3.0). Correlations between drug clearance and CYP3A4 interaction potential and between drug clearance and toxicity were performed by Kruskal-Wallis analysis of variance by ranks with post-hoc analysis using an all Pairs Tukey-Kramer test. The *a priori* level of significance was $P<0.05$.

Results

Patient characteristics

AMC034 enrolled 110 patients at 20 sites between December 2002 and April 2006, of whom 106 were treated and included in this analysis (Figure 1). Seventy-five patients were taking cART during treatment: 35 on DA-EPOCH-R and 40 on DA-EPOCH→R. Patient characteristics are presented in Table 1. The concurrent cART and without cART groups did not differ significantly in gender, age, or histology. Baseline median CD4 count were comparable between the two groups (198 cells/ μ L vs 188 cells/ μ L; $P=0.28$). Baseline CD4 counts were less than 100 cells/ μ L in 35% of patients on concurrent cART and 23% of patients not on cART. Of the 31 patients in the without cART group, 6 (19%) started cART within 8 weeks of receiving the last cycle of chemotherapy; none of the patients initiated cART during chemotherapy.

Pre-chemotherapy cART, CD4 count, and HIV viral load

We further defined patients as belonging to a *pre*-chemotherapy cART group if they received a cART regimen for at least 3 months at any point in their lifetime prior to clinical trial enrollment. Overall, 44 patients (42%) had pre-chemotherapy cART: 26 (48%) in the concurrent cART group and 8 (26%) without cART group. Forty-two patients with pre-chemotherapy cART had CD4 counts available, and 41 had HIV VL data available. Among patients without pre-chemotherapy cART, 62 had CD4 counts and 56 had HIV VL data available. At baseline, the median CD4 count for patients on pre-chemotherapy cART was significantly greater than for patients not on prior cART (245 cells/ μ L vs 164 cells/ μ L; $P=0.043$). The median HIV VL for patients on pre-chemotherapy cART was significantly less than for patients not on prior cART (639 copies/mL vs 31644 copies/mL; $P<0.001$).

Within the concurrent chemotherapy and cART group, the baseline median CD4 count for patients not on pre-chemotherapy cART was 167 cells/ μ L, while it was 234 cells/ μ L for those on pre-chemotherapy cART. Similarly, the median HIV VL for patients in the concurrent cART group without pre-chemotherapy cART was 14,250 copies/mL, while those with pre-chemotherapy cART had a median VL of 493 copies/mL.

Treatment administered

The median number of cycles and cyclophosphamide dose received (mg/m²) are summarized in Table 2. There was no difference in the number of cycles (4.0 vs 5.0; $P=0.49$)

or the median cyclophosphamide dose (367 mg/m^2 vs 413 mg/m^2 ; $P=0.32$) between the group receiving cART and the group without cART.

Relation between CD4 count and cART

Patients receiving concurrent cART had a numerical decrease in the median CD4 count after two cycles of treatment compared to baseline ($198 \text{ cells/}\mu\text{L}$ vs $162 \text{ cells/}\mu\text{L}$; $P=0.30$), but the count returned to pretreatment baseline when measured one month post-treatment ($198 \text{ cells/}\mu\text{L}$ vs $208 \text{ cells/}\mu\text{L}$; $P=0.38$; Figure 2), although the changes were not statistically significant. In contrast, for patients not on cART, the CD4 count continued to decline significantly from baseline one month post-treatment ($188 \text{ cells/}\mu\text{L}$ vs $97 \text{ cells/}\mu\text{L}$; $P=0.024$). There was a significant difference in the CD4 count at one month post-treatment from baseline between the cART and without cART groups ($P=0.004$; Figure 2). Moreover, only 19% of patients on cART while 36% of patients without cART had a continued decrease in their CD4 count one month post-treatment compared to their CD4 count during chemotherapy (Supplemental Table 1S).

At 3 and 6 months post-treatment, the CD4 count increased in both groups. However, the CD4 count for patients on cART rose to levels significantly higher than baseline by six months post-EPOCH ($198 \text{ cells/}\mu\text{L}$ vs $234 \text{ cells/}\mu\text{L}$; $P=0.005$). In contrast, the median CD4 count for patients not on cART increased to values comparable to baseline six months after completing chemotherapy ($188 \text{ cells/}\mu\text{L}$ vs $200 \text{ cells/}\mu\text{L}$; $P=0.52$).

Findings for dynamic changes of CD8 counts on and off cART during chemoimmunotherapy can be found in the supplemental text.

Relation between HIV viral load and cART

At baseline, the median HIV VL in patients receiving cART was less than that in patients without cART (5530 copies/mL vs 37786 copies/mL ; Figure 3). Patients on concurrent cART had a significant decrease in the median HIV VL, even during treatment (5530 copies/mL vs after two cycles 400 copies/mL ; $P<0.001$). Compared to baseline, the VL continued to decrease one, three, and six months post-treatment (5530 copies/mL vs 93 copies/mL vs 63 copies/mL vs 75 copies/mL ; $P<0.001$). In contrast, patients not on cART had a numeric increase in HIV VL after cycle 2 of EPOCH (37786 copies/mL vs 57500 copies/mL ; $P=0.12$) that continued 1 month post-treatment (37786 copies/mL vs 56129 copies/mL ; $P=0.86$), although the change was not statistically significant. However, the VL decreased significantly at three and six months post-treatment for the group not on cART to 629 copies/mL and 400 copies/mL , respectively, likely due to recommended post-chemotherapy cART initiation ($P<0.001$).

Relation between cART and pharmacokinetics

Pharmacokinetic data was available on 50 and 61 patients for doxorubicin and etoposide, respectively. Etoposide ($P=0.35$) clearance was similar regardless of the cART regimen (Table 3). Doxorubicin clearance differed between the CYP3A4 inducers and inhibitors ($P=0.03$; Table 3).

Relation between cART and treatment outcomes

The relationship of concurrent cART with response to anti-lymphoma therapy and survival is presented in Table 4 and figures 4 and 5. CR was observed in 43 of 75 patients receiving concurrent cART and 21 of 31 patients not on cART (57% vs 68%, $P=0.39$). For patients on cART, 58 of 75 had a response (ORR 77%) versus 25 of 31 (ORR 81%) not receiving cART ($P=0.80$). In multivariate analysis, the CR and OR rates were not associated with the use of cART with chemotherapy ($P=0.35$ and $P=0.74$, respectively). Concurrent cART was not associated with 1-year EFS (HR 1.00; 95% CI, 0.46–2.18; $P=0.75$) or OS (HR 1.13; 95% CI, 0.54–2.35; $P=0.97$). Findings regarding cART and outcomes subdivided by treatment arms (DA-EPOCH-R vs. DA-EPOCH→ R) were similar and can be found in supplemental table 3S.

Concurrent cART and safety

We evaluated the relationship between various grade 3 and 4 adverse events (AEs) during chemotherapy with cART (Table 5). Among the patients who were on cART, 57% on DA-EPOCH-R and 55% on DA-EPOCH→ R experienced grade 3 or 4 hematologic events. For patients without cART, 50% on DA-EPOCH-R and 40% treated with DA-EPOCH→R had grade 3 or 4 hematologic events (Table 4S). cART during chemotherapy did not increase the incidence of grade 3 or 4 hematologic AEs ($P=0.39$). Doxorubicin and etoposide clearance were not associated with grade 3 or 4 hematologic AEs ($P=0.14$ and $P=0.83$, respectively).

Two patients experienced grade 3 or 4 peripheral neuropathy during treatment; both received concurrent cART. However, there was no association between neuropathy and concurrent cART ($P=1.00$); doxorubicin ($P=0.49$) and etoposide ($P=0.51$) clearance and neuropathy also were not associated.

Grade 3 or 4 infectious complications, including OI, occurred in 31% of patients. Among patients treated with DA-EPOCH-R, 29% on concurrent cART vs. 44% without cART had grade 3 or 4 infectious AEs. OIs occurred in seven patients (9%) in the concurrent cART group and two individuals (6%) without cART. Since this was not a secondary end-point, specific OIs were not reported. Overall, concurrent cART was not associated with grade 3 or 4 infectious complications during treatment ($P=1.00$). Moreover, doxorubicin and etoposide clearance were not associated with grade 3 or 4 infectious AEs ($P=0.13$ and $P=0.50$, respectively).

The results for grade 3 and 4 hematologic, infectious and neurologic complications that occurred during the entire study period were similar to results during active treatment and can be found in the supplemental material (Supplemental Table 5S and 6S).

Discussion

We analyzed prospectively collected data from a single clinical trial, AMC034, to evaluate the dynamics of HIV VL, CD4 and CD8 counts in patients with HIV-associated B-cell NHL treated with DA-EPOCH, as well as the potential impact of concurrent cART on outcomes and drug interactions. Both groups had a decline in CD4 count during chemotherapy. However, patients without cART had a delayed recovery of CD4 count with a continued

decrease in CD4 count 1 month post-chemotherapy. At this time point, only 28% of patients on cART had a decrease in their CD4 count compared to 42% of patients not on cART. Although both groups had an increase in their CD4 count at 6 months post-treatment, the CD4 count for patients on concurrent cART rose to levels significantly higher from baseline than the non-cART group. We observed a similar trend in the CD8 counts. Furthermore, patients on concurrent cART had a significant decrease in the HIV VL even during treatment with continued decline at one, three, and six months post-treatment, whereas the group without concurrent cART had an increase in VL during treatment and at one-month post-EPOCH. However, concurrent cART was not associated with improved treatment outcome.

We observed temporal trends for CD4 and CD8 counts similar to findings reported on the effect of chemotherapy on the immune function in both immunocompetent cancer patients and individuals with HIV-associated lymphoma.(23–27) Mackall *et al* found that with progressive cycles of chemotherapy CD4 and CD8 counts declined in immunocompetent patients, including patients with NHL.(23) All patients had persistently low counts (CD4 < 200 cells/ μ L) for at least four months, and several did not have complete CD4 recovery 12 months post-chemotherapy. Similarly, patients with breast cancer receiving chemotherapy experienced suppressed CD4 counts for more than 12 months after chemotherapy.(24)

In PLWH, Little *et al* previously reported that suspension of cART during DA-EPOCH caused the CD4 count to significantly decline to nadir by cycle 6 followed by recovery to baseline values 6 to 12 months after treatment completion and reinstitution of cART.(27) OIs occurred in 8% of patients within the first three months of completing chemotherapy. Powles *et al* reported a significant decline in CD4 count during the first three months of chemotherapy for HIV-associated NHL or Hodgkin lymphoma patients on concurrent cART.(25) They also found that the CD4 count recovered to pre-chemotherapy levels within one month post-chemotherapy and rose to levels higher than baseline at three months post-treatment. This recovery is faster than previously described in patients with HIV-associated lymphoma who were not receiving concurrent cART.(27–29) This is consistent with our observation that concurrent cART during chemoimmunotherapy allows for early immunologic recovery of CD4 and CD8 lymphocytes, which may minimize the risk of OIs and contribute to an anti-lymphoma effect.(30)

Combining cART with treatment regimens for various HIV co-infections, such as tuberculosis (TB), has been shown to improve survival.(31, 32) These studies dispelled initial concerns that concomitant administration of antituberculosis and antiretroviral treatment would result in overlapping toxicities, low adherence, and increased incidence of immune reconstitution inflammatory syndrome. Early initiation of cART during treatment for TB significantly decreased the incidence of HIV progression with improvement in immune function and without increased toxicity.

In contrast to a large meta-analysis of 1,546 patients by Barta *et al*, we found no association between concurrent cART and treatment outcomes for HIV-associated B-cell NHL.(15) This meta-analysis, which included patients from AMC034, demonstrated that concomitant use of cART was associated with improved CR rates and a trend toward improved OS in patients with HIV-associated NHL.(15) In our single prospective study, the OR and CR rates were

comparable between patients receiving cART and those not on cART during treatment. We also found no association between OS or 1-year EFS and concurrent cART. This difference could be due to the much smaller sample size evaluated in our study and a consequent lack of power, which may have influenced our findings, or possibly the efficacy of DA-EPOCH with rituximab. However, we also noted no significant association between cART and various grade 3 and 4 toxicities, indicating that the concomitant use of cART with chemoimmunotherapy was well-tolerated overall.

For reasons outlined above, the use of cART with chemoimmunotherapy remains controversial and some experts argue that cART should be suspended during treatment.(13, 14, 33) The Strategic Management of Antiretroviral Therapy (SMART) group demonstrated that continuous cART decreased the risk of opportunistic disease or death compared to episodic use, which involved stopping and restarting therapy based on the CD4 count.(34) This finding was likely due to lowering of CD4 count and increasing HIV VL with episodic cART. In an international, randomized study, the INSIGHT START study group demonstrated the importance of early and continuous uninterrupted cART in decreasing the risk of serious AIDS-related and serious non-AIDS-related events.(35) Ratner *et al* reported that the combination of cART and chemotherapy (modified CHOP and full-dose CHOP) was safe in terms of pharmacokinetics.(36) The doxorubicin clearance was similar to historical controls, but cyclophosphamide clearance was 1.5-fold reduced compared to control values. In this study, we only observed a statistically significant difference in doxorubicin clearance, which with a post-hoc analysis revealed no differences between the antiretroviral groups; in addition, this difference was not correlated with clinical outcomes (e.g., toxicity) to preclude safe administration of EPOCH.

Several studies have shown that cART can be safely administered with chemotherapy, which is consistent with our findings.(29, 36, 37) However, detailed interactions between different ART classes with chemotherapeutic agents were not as comprehensively assessed as in our study. While we observed no alterations in drug tolerability or efficacy that could be explained by drug-drug interactions in this trial, strong CYP3A4 inhibitors such as ritonavir or cobicistat are no longer recommended in an antiretroviral regimen for patients undergoing chemotherapy due to concerns about increased toxicity presumed to be due to drug-drug interactions. Fortunately, more antiretroviral agents are now available with fewer drug interactions than previously used, including newer integrase inhibitors, such as dolutegravir, which have minimal drug interactions and are ideal antiretroviral agents to anchor regimens given concurrently with chemotherapy. Furthermore, the addition of cART to chemotherapy can potentially reduce the risk of OIs during and shortly after chemotherapy. In the pre-cART era, the incidence of AIDS-defining OIs was about 20%, limiting chemotherapy dosing and administration.(38) A retrospective study demonstrated significantly lower rates of OIs and mortality in patients receiving cART with chemotherapy compared to patients without cART (18% vs 52%, $P = 0.001$). (37) In patients with low CD4 count and prior OI, continuation of cART during chemotherapy may be particularly beneficial. Moreover, antiretroviral agents that induce doxorubicin clearance should be avoided given the possibility of reduced efficacy. Consultation with a specialist with expertise in cART and chemotherapy interactions is necessary for determining the optimal cART regimen to be given with concurrent chemotherapy.

We note several limitations to our analysis of AMC034. The use of concurrent cART was not uniformly prescribed in AMC034. Guidelines for starting cART have also evolved since the AMC034 trial was conducted. Prior World Health Organization (WHO) guidelines recommended that cART should not be initiated if the CD4 count was > 350 cells/ μ L. In AMC034, the median CD4 count of patients on cART was lower than in patients not on concurrent cART. This may have biased results since patients with CD4 count < 100 cells/ μ L are at a greater risk of developing infectious complications and dying.(15, 16, 39) Furthermore, patients on the sequential arm received rituximab after completing chemotherapy, which may have by itself affected the CD4 and CD8 counts. Our study was also limited by the number of patients who did not have CD4 and CD8 counts and HIV VL available during post-chemotherapy follow-up. In the cART group, 66 (88%) patients had CD4 count and 62 (83%) patients had HIV VL data available, while in the non-cART group, 25 (81%) patients had CD4 count and HIV VL available during the follow-up period. No information on CD4 or CD8 counts was available after six months, and delayed immune recovery in patients not on cART as described by Little *et al* would have been missed. Lastly, our analysis may have been underpowered and unable to detect subtle differences in outcomes given the small patient numbers in each group.

In conclusion, concurrent cART with chemoimmunotherapy is well-tolerated and allows for faster recovery of immune function, specifically CD4 and CD8 T-cell populations. While we could not demonstrate any overt benefit in lymphoma-specific outcomes or OS, our study showed no increased toxicity from concurrent cART and chemotherapy. Moreover, evidence from large retrospective studies suggests a benefit from early initiation of cART. Thus, we conclude that the preponderance of evidence is in favor of combining cART with chemotherapy. Our opinion is supported by guidelines, specifically the British HIV Association Guidelines,(40) which are admittedly based mainly on expert opinion and meta-analysis results rather than level 1 evidence from randomized clinical trials. This has far reaching implications if HIV-positive patients will be increasingly enrolled in general population studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Consort diagram

*denotes patient withdrawal; R, rituximab; DA-EPOCH includes infusional etoposide, prednisone, infusional vincristine, cyclophosphamide, infusional doxorubicin; cART, combination antiretroviral therapy.

Figure 2.

Median CD4 count during and post-treatment

*P-values obtained through Wilcoxon rank sum test comparing the change in median CD4 count at each time point from baseline between with cART and without cART groups

Figure 3.

Median HIV viral load during and post-treatment

*P-values obtained through Wilcoxon rank sum test comparing the change in median HIV viral load at each time point from baseline between with cART and without cART groups

Figure 4.
Event free survival by cART group

Figure 5.
Overall survival by cART group

Table 1

Patient clinical characteristics

	With cART	Without cART	All	P-values
No. treated	75	31	106	
Gender				
Male	65 (87%)	26 (84%)	91 (86%)	0.76
Age, median (range)	42 (22–76)	45 (23–63)	44 (22–76)	0.13
Pre-chemotherapy cART*	36 (48%)	8 (26%)	44 (42%)	
Median baseline CD4 count (cells/ μ L)	198 (2–1488)	188 (11–992)	195	0.28
CD4 count < 100 cells/ μ L	26 (35%)	7 (23%)	33 (31%)	0.26
Lymphoma histology				0.14
Diffuse large B-cell	60 (80%)	20 (65%)	80 (76%)	
Burkitt/Burkitt-like or other**	15 (20%)	11 (36%)	26 (25%)	
Stage III–IV	57 (76%)	27 (87%)	84 (79%)	0.29
Elevated LDH	50 (67%)	22 (71%)	72 (68%)	0.62
ECOG PS 2	16 (21%)	9 (29%)	25 (24%)	0.45
Age-adjusted IPI***				1.00
0 or 1 risk factor	26 (35%)	10 (32%)	36 (34%)	
2 or 3 risk factors	49 (65%)	21 (68%)	70 (66%)	
Treatment arm				0.67
DA-EPOCH-R	35 (47%)	16 (52%)	51 (48%)	
DA-EPOCH→R	40 (53%)	15 (48%)	55 (52%)	
Race				0.10
Caucasian	48 (64%)	21 (68%)	69 (65%)	
African American	23 (31%)	5 (16%)	28 (26%)	

* Pre-chemotherapy cART defined as individuals who were exposed cART for at least 3 months at any point in their lifetime prior to clinical trial enrollment.

** “Other” histologies included malignant lymphoma, not otherwise specified.

ECOG PS, Eastern Cooperative Oncology Group performance status

R, rituximab; DA-EPOCH includes infusional etoposide, prednisone, infusional vincristine, cyclophosphamide, infusional doxorubicin

*** aalPI, age-adjusted International Prognostic Index (adverse risk factors include stage III or IV disease, elevated serum lactate dehydrogenase above normal, and ECOG PS 2)

Table 2

Median number of cycles and cyclophosphamide dosing

	With cART (n = 74)	Without cART (n = 29)
Median number of cycles	4.0 (0–7)	5.0 (0–7)
Median cyclophosphamide dosing (mg/m ²)	367.4 (273.4 – 448.5)	413.0 (283.7 – 505.4)

Table 3

Doxorubicin and etoposide clearance in the presence or absence of cART

cART containing regimen	Doxorubicin (L/hr)	Etoposide (L/hr)
None or non-interacting antiretroviral	51.6±45.8 (n=26)	2.75±1.63 (n=30)
CYP3A4 inducer	37.1±29.5 (n=12)	3.65±2.64 (n=13)
CYP3A4 inhibitor	82.8±51.6 (n=11)	2.61±2.11 (n=16)
Mixed (both CYP3A4 inducer and inhibitor)	36.7 (n=1)	1.07, 1.61 (n=2)

Table 4

Response data by cART group

Outcome	With cART (n = 75)	Without cART (n = 31)	p-value
Overall Response, n (95% CI)	58 (77%)	25 (81%)	0.80 [*]
Complete Response, n (95% CI)	43 (57%)	21 (68%)	0.39 [*]
One-yr overall survival, % (95% CI)	75.4 (63.8 – 83.7)	83.3 (64.5 – 92.7)	0.96 ^{**}
One-yr EFS, %, (95% CI)	73.9 (61.7 – 82.7)	83.1 (64.0 – 92.6)	0.77 ^{**}

^{*} based on Fisher's exact test

^{**} based on log-rank test

EFS, Event-free survival

Table 5

Grade 3 or 4 adverse events by cART group that occurred during the treatment period

Grade 3 or 4 Adverse Event	With cART (n = 75)	Without cART (n = 31)	<i>p</i> -values
Hematologic, n (%) (95% CI)	42 (56%)	14 (45%)	0.39
Infection, n (%) (95% CI)	23 (31%)	10 (32%)	1.00
Neuropathy, n (%) (95% CI)	2 (3%)	0	1.00