BMT CTN 0803

High Dose Chemotherapy with Autologous Stem Cell Rescue for Aggressive B Cell Lymphoma and Hodgkin Lymphoma in HIV-infected Patients

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BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

High Dose Chemotherapy with Autologous Stem Cell Rescue for Aggressive B Cell Lymphoma and Hodgkin Lymphoma in HIV-infected Patients

BMT CTN PROTOCOL 0803 (AMC-071) VERSION 2.0

Study Chairpersons

Joseph Alvarnas, M.D.[1]
Richard Ambinder, M.D.[2]

Protocol Team

Gorgun Akpek, M.D., M.H.S.[3]
Robert Baiocchi, M.D., PhD.[4]
Shelly Carter, Sc.D.[5]
Steve Devine, M.D.[4]
Charles Flexner, M.D.[2]
Steve Forman, M.D.[1]
Mary Horowitz, M.D, M.S.[6]
Heather Jacene, M.D.[2]
Rick Jones, M.D.[2]
Lawrence Kaplan, M.D.[7]
Amrita Krishnan, M.D.[1]
Jennifer Le-Rademacher, Ph.D.[6]
Alexandra Levine, M.D.[1]
Richard Little, M.D.[8]
Brent Logan, Ph.D.[6]
Richard Maziarz, M.D. [9]
Willis Navarro, M.D. [10]
Uday Popat, M.D.[11]
Jason Thompson[5]
Aruna Subramanian, M.D.[2]
John Zaia, M.D.[1]

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[1]City of Hope National Medical Center
[2]Johns Hopkins Medical Institutions
[3]University of Maryland Medical Center
[4]The Ohio State University Medical Center
[5]The EMMES Corporation
[6]Medical College of Wisconsin
[7]University of California, San Francisco
[8]National Cancer Institute
[9]Oregon Health and Science University
[10]National Donor Marrow Program
[11]The University of Texas M.D. Anderson Cancer Center

Core Study Participants:

City of Hope National Medical Center
Johns Hopkins Medical Institutions
University Hospitals of Cleveland, CWRU
University of California, San Diego
University of Minnesota
University of Texas, MD Anderson Cancer Center

Affiliate Study Participants:

Ohio State University Medical Center
Virginia Mason Medical Center

PROTOCOL SYNOPSIS - BMT CTN PROTOCOL #0803

High Dose Chemotherapy with Autologous Stem Cell Rescue for Aggressive B Cell Lymphoma and Hodgkin Lymphoma in HIV-infected Patients

Study Chairpersons: Joe Alvarnas, M.D. and Richard Ambinder, M.D.

Primary Objective: The primary objective of this multi-center study is to assess the overall survival after autologous hematopoietic stem cell transplantation (HCT) for chemotherapy-sensitive aggressive B cell lymphoma or Hodgkin's lymphoma in patients with HIV using BEAM for pre-transplant conditioning.

Secondary Objectives: Patients will be assessed for the following endpoints:

1. Time to progression
2. Progression-free survival
3. CR and CR+PR proportion at Day 100
4. Time to progression after CR
5. Lymphoma disease-free survival
6. Time to hematopoietic recovery
7. Hematologic function at Day 100
8. Toxicities
9. Incidence of infections
10. Treatment-related mortality
11. Immunologic reconstitution
12. Assessment of the impact of therapy on the HIV reservoir
13. Assessment of microbial gut translocation
14. Assessment of DNA in blood (clonal Ig DNA in plasma, EBV DNA in plasma and PBMC) as tumor markers will be assessed.

Study Design: This study is designed as a Phase II multi-center trial.

Accrual Objective: The trial will accrue 40 patients.

Accrual Period: The estimated accrual period is two years.

Eligibility Criteria: Eligible patients are a minimum of 15 years of age with Karnofsky performance status ≥ 70% that have persistent or recurrent diffuse large B-cell, immunoblastic, plasmablastic, Burkitt's or Burkitt-like, or classical Hodgkin lymphoma. Patients must have received 1-3 prior treatment regimens, including an induction chemotherapy and ≤ 2 salvage regimens. Monoclonal antibody therapy and local radiation will not be counted as prior therapies. Patients must have chemosensitive disease as demonstrated by response to induction

or salvage chemotherapy. Patients must also have ≤ 10% bone marrow involvement after their most recent salvage therapy. Patients cannot have had prior autologous or allogeneic HCT. Patients must initiate conditioning therapy within 3 months of mobilization or bone marrow harvest. Mobilization therapy may be employed per institutional guidelines. Patients must have an adequate autograft to be eligible for the protocol. Patients may not have HIV refractory to pharmacologic therapy. Patients must not have opportunistic infection that is not responding to therapy.

Treatment Description: Patients will receive BCNU 300 mg/m^2 Day -6, Etoposide 100 mg/m^2 BID Days -5 to -2, Cytarabine 100 mg/m^2 BID Days -5 to -2, and Melphalan 140 mg/m^2 Day -1 followed by autologous HCT.

Study Duration: Patients will be followed on study for two years post-HCT.

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. NHL and Hodgkin Lymphoma in Patients with HIV Infection

Non-Hodgkin lymphoma (NHL) is an AIDS-defining diagnosis for patients infected with the Human Immunodeficiency Virus (HIV). While the incidence of NHL has decreased amongst HIV-infected patients since the advent of highly-active anti-retroviral therapy (HAART), lymphoma remains a significant cause of death for this patient population.[1, 2, 3] The majority of patients with AIDS-related lymphoma have B-cell malignancies that include common entities such as diffuse large B-cell lymphoma, Burkitt lymphoma and Burkitt-like lymphoma as well as less common clinical entities such as primary effusion lymphoma, plasmablastic lymphoma and primary central nervous system lymphoma.[4]

The prognosis for patients with AIDS-related lymphoma is dramatically different in the era of HAART therapy. In a comparison of treatment outcomes for patients treated before and after the advent of HAART, there is a statistically significant improvement in the overall survival of patients treated with HAART ($p = 0.002$). While the International Prognostic Index (IPI) remains a useful tool for estimating the prognosis of patients with AIDS-related NHL, the CD4 count of less than 100 per microliter has independent prognostic value for this group of patients.[1] The impact of HAART therapy upon the immunological and functional status of patients with HIV infection has permitted the extension of aggressive therapeutic regimens to this patient population. Amongst HAART-treated patients with diffuse large B-cell lymphoma, the outcome for treatment using CHOP or rituximab-CHOP appears to be similar to that for patients without HIV infection.[5, 3, 6] Similarly, HIV patients with Burkitt or Burkitt-like lymphomas may be treated with intensive immunochemotherapeutic regimens similar to those utilized for patients without HIV infection.[7, 8, 9] While toxicities are somewhat greater for those patients with AIDS, treatment outcomes appear to approach those achieved in patients without HIV-infection.[8]

Unfortunately, despite considerable advances in the treatment of AIDS-related NHL, induction-failure and disease relapse remain key challenges. In a retrospective evaluation of 111 patients with AIDS-related NHL treated following the availability of HAART, patients were evaluated based upon IPI score and CD4 count at the time of diagnosis. For patients in the two highest risk quartiles at the time of diagnosis, the 1-year survival rates were only 20% and 15% respectively.[1] In another trial comparing outcomes for patients prior to and subsequent to the availability of HAART, the median survival for patients with diffuse large B-cell lymphoma and Burkitt lymphoma treated in the post-HAART era was only 38.1 months and 5.1 months, respectively.[3]

While Hodgkin lymphoma is not an AIDS-defining diagnosis, the incidence of this disease is increased amongst patients with HIV infection.[2, 3] Hodgkin lymphoma is the third most common non-AIDS-defining malignancy amongst patients with HIV infection.[10] Hodgkin lymphoma occurs more frequently in HIV infected patients than the general population with a standardized risk ratio of 14.7 (95% CI, 11.6-18.2). The survival for this group of patients has improved in

the HAART era, but a review of 47 patients diagnosed between 1997 and 2001, the estimated 2-year overall survival was only 62%.[11]

1.2. Autologous Hematopoietic Cell Transplantation for Patients with HIV Infection

The prognosis for patients with refractory and relapsed NHL is poor with overall survival rates of less than 20% for patients treated with non-transplant salvage therapies. Based upon a randomized trial and numerous phase II trials, high-dose therapy with autologous hematopoietic cell transplantation (HCT) has been established as the standard of care for patients with chemotherapy-sensitive relapsed non-Hodgkin lymphoma.[12, 13, 14]

The use of autologous HCT for a patient with AIDS-related lymphoma was initially published as a case report in 1996.[15] This initial transplant experience was marked by what appeared to be an increased risk of opportunistic infection. Since the available of HAART, however, the transplant experience has evolved considerably and several groups have now demonstrated the feasibility of performing high-dose therapy with autologous HCT in patients with HIV-related Hodgkin and non-Hodgkin lymphoma.

In a trial published by City of Hope, patients with induction-failure NHL, chemotherapy-sensitive disease and IPI high-risk disease for eligible for treatment. Twenty patients were enrolled in the trial, including 4 with IPI high-risk disease and 2 patients with Hodgkin lymphoma. All of the patients successfully achieved adequate autologous stem cell collections. Patients were treated either with high-dose chemotherapy (17 patients - carmustine, etoposide, cyclophosphamide) or intensive chemo-radiotherapy (3 patients - fractionated total body irradiate, etoposide, cyclophosphamide). One patient died of regimen-related toxicity and 2 patients suffered early relapses of their disease. At a median follow-up of 31.8 months, 17 of 20 patients were alive and free of evidence of disease. Treatment-related complications were comparable to those seen in the non-HIV-infected patient population.[16]

In a trial published by the AIDS Malignancy Consortium, 27 patients with either AIDS-related NHL or Hodgkin lymphoma in the setting of HIV infection were enrolled.[17] Twenty patients, including 15 with NHL and 5 patients with Hodgkin lymphoma, subsequently underwent autologous HCT using a preparative regimen that consisted of dose-reduced busulfan and cyclophosphamide. One patient died of regimen-related toxicity. At a median follow-up time of 23 weeks, 10 patients were alive and free of disease.

Re, et al described a group of patients with HAART-responsive HIV infection and either relapsed or refractory NHL (8) or Hodgkin lymphoma (8) who enrolled on trial. Twelve patients collected an adequate stem cell dose. One patient suffered disease progression prior to transplant. Ten patients underwent autologous HCT following preparation with the BEAM (carmustine, etoposide, cytarabine, melphalan) regimen.[18] Patients continued HAART throughout the entire treatment regimen. All patients achieved engraftment post-transplant and there were no regimen-related deaths. The 2-year estimated overall survival at a follow-up of 18 months was 39.3% +/- 18.9%.

Several other groups have demonstrated the feasibility of performing autologous HCT in this patient population. Gabarre, et al. reported the results of autologous HCT for 14 HIV-infected patients with relapsed or refractory NHL (8) or Hodgkin lymphoma (6).[15] At the time of transplant, 11 patients had either achieved a complete or partial remission and 3 demonstrated evidence of progressive disease. At 1 month post-transplant, 10 patients were in complete remission. At the time of the study publication, 5 patients remained alive, including 4 in complete remission. Serrano, et al. reported on 14 patients who underwent autologous HCT for AIDS-related lymphoma.[19] All patients collected adequate numbers of stem cells. Eleven patients underwent transplant and there was no transplant-related mortality. At a median follow-up of 32 months, 8 patients remained alive in complete remission.

More recently, the EBMT Lymphoma Working Party published treatment outcomes for 68 patients with HIV-related lymphoma (including 18 patients with Hodgkin lymphoma) that underwent autologous HCT.[20] Patients were treated at 20 different institutions. Sixty-five patients were treated with the BEAM regimen and the remainder was treated with radiation therapy-based regimens. At a median follow-up of 32 months, the 3-year estimated progression-free and overall survivals for the group were 56% and 61%, respectively. Overall cumulative incidence of non-relapse mortality was 4.4% and 7.5%, at three and 12 months respectively. Relapse or progression was identified in 20 patients after a median time of 4.1 months from autologous HCT with the predicted cumulative incidence of relapse of 30% at 24 months. Multivariate analyses of these outcomes suggested that a) age > 50 years at autologous HCT was the only independent adverse prognostic factor for non-relapse mortality, b) histology, use of more than two chemotherapy regimens prior to autologous HCT and not being in remission at the time of autologous HCT were associated with increased risk of relapse, and c) not achieving complete remission in having chemotherapy resistant disease at autologous HCT were associated with worse progression free survival and overall survival. A subsequent EBMT study reported the results of a matched case control study of outcomes of Hodgkin's disease and non-Hodgkin's lymphoma patients undergoing autologous HCT stratified by HIV^+ status.[21] The results of this comparative study revealed that HIV^+ patients undergoing autologous HCT for lymphoma had similar relapse rates, progression free survival and overall survival. There was a slight increase in non-relapse mortality at one year in HIV^+ lymphoma patients versus those who were HIV^- (8% vs. 2%), but this difference did not reach statistical significance.

In sum, the probability of survival after high-dose conditioning followed by autologous stem cell transplantation ranges between 39% to 85% as seen in Table 1.2.

TABLE 1.2 CUMULATIVE OUTCOME AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH HIV-ASSOCIATED NHL AND HL

Reference	Failed to Mobilize (n)	Patients Transplanted (n)	TRM	Median follow-up (months)	Patients Surviving (%)
Krishnan	0	20	5%	32	85
Spitzer	2	20	5%	5.8	50+??
Re	4	10	0%	18	39
Gabare	?	14	?	1	71
Serrano	0	11	0%	32	73
EBMT	NA	68	7.5%	32	61

1.3. HIV Infection and Risk of Opportunistic Infection following Autologous HCT

Prior to the advent of HAART, opportunistic infection was a key limitation to the use of autologous HCT for patients with HIV-related lymphoma. In the evolving transplant experience in the era of HAART, opportunistic infection has not proven to be a significant limitation to the use of high-dose therapy. In the City of Hope group, Gabarre et al and AIDS Malignancy Consortium trial, CMV reactivation was noted in 3, 2 and 4 patients, respectively.[16, 17, 22]

A key finding in the transplant experience to date has been that with availability of HAART, uncontrolled HIV infection has not been a significant transplant-related complication. Even amongst those groups in which HAART therapy was withheld on a planned basis during the peri-transplant period, most patients were able to achieve suppression of HIV to undetectable levels by the end of the first post-transplant year.[16] Similarly Gabarre, et al noted marked viral suppression in evaluable patients by 2 years post transplant.

CD4 reconstitution following transplant appears comparable between groups. The City of Hope group, the AIDS Malignancy Consortium trial and Gabarre, et al all have noted a decrement in the CD4 count that occurs through the 3rd transplant month, followed by a progressive rise in the median CD4 counts through the first and second post-transplant years.

1.4. New Frontiers

As the safety of HIV auto transplants have gained acceptance, new questions have emerged with regard to aspects of HIV biology, HIV lymphoma tumor markers, and the relationship between gut and liver dysfunction that can be uniquely addressed in the context of a trial involving high dose myeloablative chemotherapy.

1.4.1. HIV Single Copy PCR

In patients with undetectable viral load as measured in conventional assays, there may be persistent viremia that can be measured at single copy/ml by specialized PCR analysis. This

viremia may reflect virus being released by the decay of latently infected cells or possibly ongoing viral replication.

1.4.2. Immune Reconstitution

The dynamics that occur with adaptive, innate, and humoral immune networks during and after stem cell engraftment in patients with AIDS-related Lymphoma (ARL) remain poorly characterized. These studies will address immune reconstitution that occurs during and after engraftment of autologous stem cells in patients with HIV. Examining the nature of adaptive immune reconstitution will involve use of a multi panel flow cytometric assay to track changes in naïve, memory, activated and regulatory T cell subsets. Parallel studies will evaluate adaptive responsiveness to viral recall antigens (CMV, EBV and HIV pooled peptides). Innate immune reconstitution studies will examine natural killer (NK) cell subsets with a multi panel flow cytometric assay as well as address NK cell cytokine and FcγRIIIa responsiveness (with IFNγ and granzyme B or CD107a as biologic readout). All of these studies have been successfully performed on peripheral blood mononuclear cell subsets that have been acquired from fresh or frozen samples in HIV- patients following allogeneic and autologous stem cell transplantation.

1.4.3. DNA in Blood

Tumor DNA detected in plasma is emerging as a potentially useful tumor marker. Two candidate tumor markers in patients with HIV lymphomas have emerged. These are: i) clonal Ig DNA as recognized by Ig rearrangements or characteristic somatic hypermutation; and, ii) EBV DNA. In a small series, clonal Ig DNA is characteristic of a particular patient's B cell tumor and is detected in approximately half of AIDS diffuse large B cell lymphoma prior to treatment. In that series, patients in whom clonal Ig DNA persists in plasma inevitably relapse. EBV DNA detected in plasma is useful as a tumor marker in nasopharyngeal carcinoma where evidence suggests that viral genomes are released from apoptotic tumor cells rather than being present as virions. In AIDS, high copy numbers of EBV genomes is present in many HIV patients and in studies from the Multi-Center AIDS Cohort Study, have demonstrated very modest value to EBV determinations. Recent evidence suggests that tumor cell derived viral DNA may be distinguished from virion DNA because virion DNA is not CpG methylated. Thus meCpG EBV DNA may specifically mark tumor DNA.

1.4.4. Microbial Translocation

Hepatic injury is one of the potentially fatal complications of high-dose and stem cell therapies. Liver disease has emerged as a leading cause of death among patients with immunodeficiency.[22] Liver disease in association with hepatitis B or C infection progresses more rapidly in HIV patients than others.[23] One of the hypothesized mechanisms has to do with HIV-related depletion of mucosal CD4 T cells with disruption of gut epithelial integrity and increased mucosal translocation (MT) of bacteria and bacterial products including LPS. Hepatic tissues are directly affected by MT. Emerging evidence also suggests that alcohol related liver injury is also linked to MT. Some evidence also suggests that graft-versus-host related liver disease and celiac liver disease are also mediated in part by microbial translocation. The proposed study would provide information about MT in association with high dose therapy in HIV patients and allow a preliminary analysis of an association with liver function abnormalities.

Recent observations that persons with chronic HIV-1 infection and AIDS demonstrate increased MT from the gut compared to uninfected persons may be related to the massive depletion of intestinal CD4+ lymphocytes within weeks of HIV-1 acquisition (1). MT in HIV-HCV co-infection was strongly associated with more rapid progression of liver cirrhosis. A key finding was that serum endotoxin (LPS) level, a marker of microbial translocation, was higher in patients with more advanced fibrosis (2). Autologous transplant patients are at risk for hepatic veno-occlusive disease (VOD). A high level of circulating MT markers (such as LPS) at the time of transplant could be a risk factor for liver damage especially in HIV patients. Moreover, monitoring serum levels temporally to explore associations with liver associated morbidity including VOD, may provide insights into defining risk factors for VOD.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

All patients will undergo an autologous HCT. Collection of an adequate graft is a prerequisite of study entry but must be not more than three months prior to start of conditioning. Pre-transplant conditioning will consist of BCNU 300 mg/m^2 on Day -6. Ara-C 100 mg/m^2 BID and VP-16 100 mg/m^2 BID will be administered on Days -5, -4, -3 and -2. Melphalan 140 mg/m^2 will be administered on Day -1 and HCT on Day 0. Patients will be followed for at least two years after enrollment.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this multi-center study is to assess the overall survival after autologous hematopoietic stem cell transplantation (HCT) for chemotherapy-sensitive aggressive B cell lymphoma or Hodgkin's lymphoma in patients with HIV using BEAM for pre-transplant conditioning.

2.2.2. Secondary Objectives

The secondary objectives are:

1. Time to progression
2. Progression-free survival
3. CR and CR+PR proportion at Day 100
4. Time to progression after CR
5. Lymphoma disease-free survival
6. Time to hematopoietic recovery
7. Hematologic function at Day 100
8. Toxicities
9. Incidence of infections
10. Treatment-related mortality
11. Immunologic reconstitution
12. Assessment of the impact of therapy on the HIV reservoir
13. Assessment of microbial gut translocation
14. Assessment of DNA in blood (clonal Ig DNA in plasma, EBV DNA in plasma and PBMC) as tumor markers will be assessed.

2.3. Patient Eligibility

Patients must meet specified eligibility criteria for entry into the study.

2.3.1 Patient Inclusion Criteria

Patients fulfilling the following criteria will be eligible for entry into this study:

1. Diagnosis of persistent or recurrent WHO classification diffuse large B-cell lymphoma, composite lymphoma with > 50% diffuse large B-cell lymphoma, mediastinal B-cell lymphoma, immunoblastic, plasmablastic, Burkitt's or Burkitt-like or classical Hodgkin's lymphoma. Patients transformed from follicular lymphoma are eligible for the study, pending fulfillment of other criteria.
2. 15 years old or older
3. Three or fewer prior regimens of chemotherapy over the entire course of their disease treatment (including one induction chemotherapy and no more than 2 salvage chemotherapies). Monoclonal antibody therapy and involved field radiation therapy will not be counted as prior therapies.
4. All patients must have chemosensitive disease as demonstrated by at least a partial response (as defined by the criteria in Chapter 3) to induction or salvage therapy.
5. $\leq$ 10% bone marrow involvement.
6. Patients with adequate organ function as measured by:
    a) Cardiac: American Heart Association Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Additionally, all patients must have a left ventricular ejection fraction at rest $\geq$ 40% demonstrated by MUGA or echocardiogram.
    b) Hepatic:
        i. Bilirubin $\leq$ 2.0 mg/dL (except for isolated hyperbilirubinemia attributed to Gilbert syndrome or antiretroviral therapy as specified in Appendix D) and ALT and AST $\leq$ 3x the upper limit of normal.
        ii. Concomitant Hepatitis: Patients with chronic hepatitis B or C may be enrolled on the trial providing the above criteria are met. In addition, no active viral replication - undetectable (viral load <500 copies/ml) hepatitis B DNA level by PCR and no clinical or pathologic evidence of irreversible chronic liver disease. See Appendix D for additional information and management guidelines.
    c) Renal: Creatinine clearance (calculated creatinine clearance is permitted) > 40 mL/min.
    d) Pulmonary: DLCO, FEV1, FVC $\geq$ 45% of predicted (corrected for hemoglobin).
7. Autologous peripheral stem cell graft with a minimum of $\geq 1.5 \times 10^6$ CD 34^+ cells/kg (target $\geq 2.0 \times 10^6$ CD 34^+ cells/kg) or if PBSC mobilization fails, **cells can be obtained by bone marrow harvest per institutional practices (in cases where bone marrow will be used for transplantation, the required CD34+ dose does not apply and institutional requirements for total nucleated cell dose should apply).**

8. Initiate conditioning therapy within 3 months of mobilization or bone marrow harvest.
9. Signed informed consent.
10. Patients on antiretroviral therapies (ARVs) can either have:
    a. Undetectable HIV viral load (VL < 50 copies).
    b. If VL detectable at < 2000 copies/mL must have review of previous antiretroviral regimens or previous genotypic or phenotypic testing which indicate the ability to fully suppress virus by addition of sensitive drugs. This review will be carried out by the ID specialist caring for the patient.
    c. If VL detectable at >2000 copies/mL, a current HIV genotype and/or phenotype must be obtained. If a HAART regimen to which the patient's virus is sensitive can be determined based on genotype and previous antiretroviral experience, then the patient will be considered eligible in this regard. This review will be carried out by the ID specialist caring for the patient.

2.3.2 Patient Exclusion Criteria

Patients with the following will be ineligible for registration onto this study:

1. Karnofsky performance score < 70%.
2. Uncontrolled bacterial, viral or fungal infection (currently taking medication and with progression or no clinical improvement).
3. Prior malignancy in the 5 years prior to enrollment except resected basal cell carcinoma, treated cervical carcinoma *in situ* or Kaposi's sarcoma.
    a. Symptomatic Kaposi's sarcoma currently requiring therapy is excluded (patients receiving topical therapy for minimal disease are not included in this definition).
    b. Prior treatment with topical agents, local radiation, or up to 6 cycles of cytotoxic chemotherapy at least six months prior is permitted.
    c. Other cancers treated with curative intent < 5 years previously will not be allowed unless approved by the Medical Monitor or Protocol Chair.
    d. Cancer treated with curative intent > 5 years previously will be allowed.
4. Pregnant (positive β-HCG) or breastfeeding.
5. Fertile men or women unwilling to use contraceptive techniques from the time of initiation of mobilization until six-months post-transplant.
6. Prior autologous or allogeneic HCT.
7. Patients with evidence of MDS/AML or abnormal cytogenetic analysis indicative of MDS on the pre-transplant bone marrow examination. Pathology report documentation need not be submitted.

2.4. Study Treatments

The immediate pre-HCT evaluation will be carried out according to the operating procedures of the participating institutions and should be in keeping with the data reporting requirements of this study. Similarly, special orders and procedures will be those defined by the BMT CTN Manual of Procedures (MOP). All patients enrolled on this protocol will be hospitalized in accordance with the procedures for recipients of HCT as defined by the treating institutions. See the conditioning regimen in Table 2.4 below.

TABLE 2.4: BEAM + HCT REGIMEN

Day						
-6	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
BCNU 300 mg/m^2	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Ara-C 100 mg/m^2 BID VP-16 100 mg/m^2 BID	Melphalan 140 mg/m^2	HCT

1. **BCNU:** 300 mg/m^2 on Day –6, to be administered per institutional guidelines.
2. **Cytarabine (Ara-C):** 100 mg/m^2 BID on Days –5 through –2, for a total of 8 doses, to be administered per institutional guidelines.
3. **VP-16:** 100 mg/m^2 BID on Days –5 through –2, for a total of 8 doses, to be administered per institutional guidelines.
4. **Melphalan:** 140 mg/m^2 on Day -1, to be administered per institutional guidelines.
5. **Conditioning Regimen Administration Schedule:** The conditioning regimen administration schedule may be modified ± 1 day according to institutional practice. Day 0 will be the day of HCT.

2.5. Supportive Care

2.5.1. Post-HCT

All supportive care will be given in keeping with BMT CTN MOP and local institutional guidelines.

2.5.1.1.Prophylaxis against infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the post-HCT period according to the BMT CTN MOP. Additional guidelines for HIV patients in this study are summarized in Appendix D.

2.5.1.2.Cryopreservation

Hematopoietic progenitor cells will be cryopreserved according to the institutional standards.

2.5.1.3.Post-HCT Growth Factors

All patients will receive G-CSF 5-10 mcg/kg beginning no later than Day +7 post-transplant until an ANC $\geq$ 500/mm^3 is obtained for 3 consecutive days. If patients fall below this level once the G-CSF has been stopped, it can be restarted.

2.5.1.4.Post-HCT Lymphoma Therapy

Consolidative localized radiation therapy (maximum 3 sites) is allowed to areas of previous bulk disease (> 5 cm). Localized radiation should be completed by Day 100 post-transplant. No other anti-lymphoma therapy is allowed in the post-transplant setting or the patient will be considered to have progressed.

2.5.1.5.Anti-Retroviral Therapy

Anti-retroviral (ARV) therapy is only effective when administered in combination and with consistency. Single agent therapy or repeated interruptions in therapy lead to resistance. The ARV guidelines below are designed to minimize the possibility of drug interactions with high dose chemotherapy and to administer ARV only when it is anticipated that the ARV regimen can be consistently complied with (i.e. preparative regimen toxicities such as nausea and mucositis will not interfere with dosing schedules).

ARV naïve patients, patients who are on ARV, and patients who are ARV experienced are eligible for the protocol.

Two ARVs require special mention: efavirenz and AZT.

Efavirenz has a long half life and resistance develops especially rapidly when it is administered in the absence of other ARVs. When an efavirenz containing regimen is stopped, levels of other ARVs will fall much more rapidly than those of efavirenz resulting in the functional equivalent of single agent therapy and risking resistance. In order to avoid this risk, another ARV should be substituted for efavirenz for at least 2 weeks before ARV therapy is stopped.

AZT is myelosuppressive and should not be used in the ARV regimen administered after HCT.

Patients on established antiretroviral regimens:

1) If patient not on efavirenz (sustiva)-containing regimen, continue the ARVs until conditioning chemotherapy is started and then discontinue all ARVs at once.
2) If patient is on efavirenz (sustiva)-containing regimen, change efavirenz to an alternative medicine (such as a protease inhibitor) for at least 2 weeks prior to starting conditioning and then discontinue all ARVs at the time of starting conditioning regimen.

3) Resume an ARV regimen at least 7 days after the preparative regimen and after mucositis has resolved and the patient is consistently able to tolerate oral medications. The ARV regimen should not include AZT.

If patient is ARV naïve:

1) Check genotype if never done previously (or obtain results of previous genotype)
Start ARV regimen that does not contain AZT based on genotype results anytime after Day 7 post transplant once mucositis is resolved and patient is able to tolerate oral medications.

2.6. Participant Risks

HCT recipients incur risks from high-dose conditioning and post-HCT therapy, which must be weighed against the risk of the disease for which the HCT is prescribed. Major risks following transplantation include: 1) Infection which can be bacterial, viral, parasitic, or fungal. Often, these infections are life-threatening, particularly when caused by viral or fungal agents, and are associated with high mortality in the transplant population. The published experience shows increased risk of CMV viremia, but no increase in mortality related to that virus; 2) Damage of all or any of the major organs may occur as a result of reactions to drugs (e.g., chemotherapy, antibiotics, anti-fungal medications), and as a result of destructive processes (e.g., infection), and may have a fatal outcome; brain damage can result in severe loss of cognitive or neurologic function; 3) Relapse or progression of lymphoma may occur, especially in patients with advanced disease status at time of treatment; 4) Unknown toxicities may occur in any individual patient due to multiple events and cumulative effects which may involve any and all organs, including the brain; and, 5) Death.

2.7. Therapy Toxicities

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. All of the following listed agents are commercially available. Please refer to www.fda.gov for full adverse event information regarding the agents listed below. All of the following agents should be administered per institutional standards, and stored per package insert instructions.

2.7.1. Carmustine (BCNU)

Carmustine is an alkylating agent. Common side effects include myelosuppression, nausea, vomiting, headache, and jaw pain. Less common side effects include transient hypotension, dizziness, hyperpigmentation of the skin, hepatoxicity and a delayed inflammatory lung response (pneumonitis).

2.7.2. VP-16 (Etoposide)

VP-16 is a semi-synthetic podophyllotoxin derivative. Side effects that are likely to occur include nausea, vomiting and diarrhea, myelosuppression, mucositis, alopecia, and fatigue. Less likely side effects include a skin rash, peripheral neuropathy, and hepatotoxicity. Hypotension

may occur if the drug is infused quickly. A rare but serious side effect is a small risk of developing a second cancer.

2.7.3. Cytarabine (Ara-C)

Cytarabine, commonly known as Ara-C, is a synthetic nucleoside. Likely side effects include myelosuppression, nausea, vomiting and diarrhea, oral and anal inflammation or ulceration, hepatic dysfunction, fever, rash, and thrombophlebitis. Less likely side effects include conjunctivitis (when Ara-C is given at high doses, and preventable by the prophylactic use of corticosteroid eye drops), abdominal pain, alopecia, pruritis, headache, and the occurrence of a cytarabine syndrome characterized by fever, myalgias, arthralgias, chest pain, maculopapular rash, conjunctivitis and malaise - this syndrome occurs 6-12 hours following drug administration. Corticosteroids are beneficial in treating this syndrome. A rare but serious side effect is cerebral/cerebellar dysfunction (more common at very high doses and in older patients).

2.7.4. Melphalan

Melphalan, an alkylating agent, is a phenylalanine derivative of nitrogen mustard. At high doses, the likely toxicities include myelosuppression, gastrointestinal toxicity and alopecia. The duration of profound myelosuppression decreases with the use of stem cell transplantation and colony stimulating factors. Gastrointestinal toxicity, which includes potentially severe stomatitis, esophagitis and diarrhea, may require intravenous narcotics for mucositis related pain, intravenous hydration and alimentation, and antibiotics. Less likely is hepatotoxicity. Rare but serious toxicities reported include pulmonary fibrosis and interstitial pneumonitis, veno-occlusive disease of the liver, skin hypersensitivity, vasculitis, hemolytic anemia, allergic reactions, and a small risk of developing second cancers.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Definition of Disease Status

Patients at each data collection period are classified into one of the following states. After HCT and until relapse/progression, all disease classifications are relative to the patient's pre-HCT disease status. Tests used for evaluation of disease status would be physical examination, laboratory testing, bone marrow biopsy and aspirate, PET scans, and CT scans of neck, chest, abdomen and pelvis as indicated.

Segments of this section are excerpts from the Bruce Cheson, et al, article "Revised Response Criteria for Malignant Lymphoma."[24]

TABLE 3.1: RESPONSE DEFINITIONS

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

** In relation to Response Definitions, be aware of HIV adenopathy, this can be avid in patients with equivocal scans.
*** Additional follow-up PET needed if 90-day results are equivocal.

Complete Remission (CR):

The designation of CR requires the following (Table 3.1):

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0cm in their short axis after treatment.
- The spleen and/or liver, if considered to be enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical exam and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
- If bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of

clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Complete Remission Undetermined (CRu):

- The use of the above definition for CR and that below for PR eliminates the category of CRu.

Partial Remission (PR):

The designation of PR requires all of the following:

- At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase should be observed in the size of other nodes, liver or spleen.
- Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules in the greatest transverse diameter.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed.
- Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one, or at most two, residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD):

Stable disease (SD) is defined as the following:

- A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
- Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD, after CR)/ Progressive Disease (PD after PR, SD):

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0cm will not be considered as abnormal for relapse or progressive disease.

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- At least a 50% increase from nadir in the SPD of any previously involved nodes or in a single involved node, or the size of other lesions (e.g, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cmin its short axis
- Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g. pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative. In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g. a trial in patients with MALT lymphoma), response should be assessed as above, but

only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

3.2. Primary Endpoints

The primary endpoint is one-year overall survival.

3.3. Secondary Endpoints

3.3.1. Time to Progression

The event is relapse/progression or receiving anti-lymphoma therapy, other than post-transplant consolidative localized radiation (maximum 3 sites) to sites of prior bulk disease pre-transplant (> 3cm). The time to this event is measured from transplant. Deaths without relapse/progression are considered as a competing risk. Surviving patients with no history of relapse/progression are censored at time of last follow-up.

3.3.2. Progression-free Survival

Patients are considered a failure for this endpoint if they die or if they relapse/progress or receive anti-lymphoma therapy, other than post-transplant consolidative localized radiation (maximum 3 sites) to sites of prior bulk disease pre-transplant (> 3cm). The time to this event is the time from transplant until death, relapse/progression, receipt of anti-lymphoma therapy, or last follow up, whichever comes first.

3.3.3. CR and CR+PR Proportion at Day 100

CR (or PR) will be assessed at Day 100.

3.3.4. Time to Progression after CR (Response Duration)

This will be assessed in patients with CR. The time to this event is measured from documentation of complete response for patients entering the trial in PR and from enrollment for patients entering the trial in CR. Patients are considered failure for this end point if they relapse after complete remission. Surviving patients with no history of relapse/progression are censored at time of last follow-up.

3.3.5. Lymphoma Disease-Free Survival

This will be assessed in patients with CR. The time to this event is measured from documentation of complete response for patients enrolling in PR and from enrollment for patients entering the trial in CR. Patients are considered failure for this end point if they die or if they relapse after complete remission. Patients with no history of relapse or death after complete remission are censored at time of last follow up.

3.3.6. Time to Hematopoietic Recovery

Time to neutrophil recovery will be the first of two consecutive days of $\geq$ 500 neutrophils/μL following the expected nadir. Time to platelet engraftment will be the date platelet count is $\geq$ 20,000/μL for the first of two consecutive labs with no platelet transfusions 7 days prior.

3.3.7. Hematologic Function at Day 100

Hematologic function will be defined by ANC>1500, Hemoglobin>10g/dL without transfusion support, and platelets>100,000and measured at Day 100 and 1 year. Use of growth factors will be noted.

3.3.8. Toxicities

Toxicities will be defined by using the version 3.0 CTCAE criteria. Only grade 3 and higher toxicities will be collected.

3.3.9. Incidence of Infections

Microbiologically documented infections will be reported by site of disease, date of onset, severity, and resolution, if any. This data will be captured via an event-driven case report form and will be collected from Day 0 until one year post-transplant.

3.3.10. Treatment-Related Mortality

Treatment-Related Mortality (TRM) is defined as death occurring in a patient from causes other than relapse or progression and will be measured at 100 days.

3.3.11. Immunologic Reconstitution

Immune reconstitution assays on peripheral blood will include (i) immunophenotypic analysis of both T and natural killer subsets; (ii) functional evaluation of adaptive and innate immune responsiveness; and (iii) quantitative immunoglobulin measurement (IgM, IgG and IgA). Studies will be performed at Days 60, 180, and 365 post-transplant. Quantitative immunoglobulin measurements (IgM, IgG and IgA) will also be performed prior to initiation of conditioning. These will be summarized at each time point using descriptive statistics.

3.3.12. HIV Single-Copy PCR

HIV RNA within 90 days prior to start of conditioning, at Day 100, 180, and 1 year post transplant will be measured. For those patients with no detectable viral RNA in their **baseline** sample using the standard clinical test performed at the clinical site, additional blood samples will be collected at two time points prior to the initiation of ablative chemotherapy (at 2 time points) and at Days 180, 365 and 730 post-transplant. Plasma aliquots from these time points will be sent for further analysis at a project laboratory for possible low-level HIV-1 viremia by a

sensitive single-copy PCR assay (capable of detecting HIV-1 RNA levels down to 1 copy per milliliter of plasma).

3.3.13. Microbial Translocation Markers

Blood specimens for microbial translocation will be collected within 1 week prior to the initiation of conditioning, on Day -3 of conditioning and Days 7, 14 and 100 after stem cell infusion.

3.3.14. Ig and EBV DNA in Blood

Blood specimens will be collected within 1 week prior to the initiation of conditioning, on Day -3 of conditioning and at 100 days, 6 months and 1 year. The presence of clonal Ig DNA in plasma will be assessed, as will EBV copy number in plasma and in PBMC at each of these time points.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

Patients will be registered using the BMT CTN Electronic Data Capture System (AdvantageEDC^{SM}). The following procedures should be followed:

1. Within 3 weeks to 1 week prior to initiation of conditioning therapy, an authorized user at the transplant center completes initial screening by entering patient demographics and Segment A of the Enrollment Form in AdvantageEDC. The eligibility screening includes questions that will verify eligibility, capture the proposed start date of conditioning, and a question confirming that the patient signed the informed consent form. The patient must also be registered with the CIBMTR and have a valid CRID number.
2. If the patient is eligible, a study number is generated.

4.2. Study Monitoring

4.2.1. Follow-up Schedule

The follow-up schedule for scheduled study visits is outlined in Table 4.2.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User's Guide. The Data Management Handbook, including the Forms Submission Schedule, is available on the homepage of the Internet data entry system.

Follow-up Visits: Follow-up visits will begin as soon as patients are enrolled onto the study. The follow-up period for Segment A is 2 years.

TABLE 4.2.1: FOLLOW-UP SCHEDULE

Study Visit	Target Day (± 2 Days Prior to Day 100 Post-ASCT) (± 28 Days After Day 100 Post-ASCT)
1 week	7 days
2 week	14 days
3 week	21 days
4 week	28 days
5 week	35 days
6 week	42 days
8 week	56 days
100 day	100 days
6 month	180 days
12 month	365 days
24 month	730 days

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User's Guide. Forms that are not entered into AdvantageEDC within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC and integrated into the Data Coordinating Center's (DCC) master database or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

Reporting Patient Deaths: Recipient Death Information must be entered into AdvantageEDC within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in AdvantageEDC.

CIBMTR Data Reporting: Centers participating in BMT CTN trials must register pre and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment of BMT CTN #0803 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post-transplant Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

4.2.2 Adverse Event Reporting

Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 at regular intervals as defined on the Form Submission Schedule.

Tables 4.2.1.2A and 4.2.1.2B summarize patient clinical assessments over the course of the study.

4.2.1.1.Evaluations prior to the HCT conditioning therapy

The following observation need to be performed within 3 months of enrollment:

1. CMV IgG, hepatitis panel (HAV Ab, HBsAb, HBsAg, HBcAb, HCVAb), HSV 1 and 2 IgG, RPRor VDRL, toxoplasma IgG, VZV IgG, and HTLV1 antibody.
2. EKG
3. PET or PET-CT scan.
4. Creatinine clearance (calculated creatinine clearance is permitted).
5. CMV PCR or antigenemia assay.
6. DLCO, FEV1 and FVC.
7. Bone marrow biopsy for pathology
8. HIV RNA, CD4 Count.
9. If the core Ab are positive, HepB DNA PCR and HepC DNA PCR
10. Ejection fraction

The following observations need to be performed within 8 weeks prior to enrollment:

1. History, physical examination, height and weight, body surface area, neurologic examination, measurement of all palpable peripheral lymph nodes and measurement of other sites of disease present on physical.
   a. Lumbar puncture(s) for determination of presence of CNS disease for non-Hodgkin's lymphoma patients only.
   b. Duration of AIDS diagnosis, history of prior opportunistic illnesses.
   c. Presence or absence of "B"-symptoms (unexplained fevers, night sweats, involuntary weight loss greater than 10% normal body weight).
   d. Medication list to include all antiviral, antibiotics and opportunistic prophylaxis.

2. β-HCG serum pregnancy test for females of childbearing potential.

The following observation will be performed 4 weeks prior to enrollment:

1. Karnofsky performance status
2. CBC with differential, platelet count, creatinine, bilirubin, LDH, alkaline phosphataseALT, AST, sodium, magnesium, potassium, chloride, and CO_2.
3. CT: CT scans of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease.

The following observations will be performed after patient enrollment and within 1 week prior to initiation of conditioning therapy:

1. Karnofsky performance status
2. CBC with differential, platelet count, creatinine, bilirubin, LDH, alkaline phosphatase, ALT, AST, sodium, magnesium, potassium, chloride, and CO_2.

The following samples should be collected after enrollment but prior to initiation of conditioning:

1. Blood samples for evaluation of quantitative immunoglobulins (IgM, IgG, and IgA). *Note: Quantitative immunoglobulins will be performed at the clinical center.*
2. Collection of additional peripheral blood samples for HIV single copy assessment in only those patients with undetectable **baseline** HIV viral levels by conventional assay (See Appendix C)
3. Microbial translocation monitoring peripheral blood sample collected within 1 week prior to initation of conditioning. (See Appendix C).
4. Future research sample collection for consenting patients (See Appendix C).
5. DNA monitoring in blood (EBV and Ig DNA) collected within one week prior to initiation of conditioning. (See Appendix C).

The following samples should be collected on Day -3 of conditioning:

1. Microbial translocation monitoring sample (See Appendix C).
2. DNA monitoring in blood (EBV and Ig DNA) samples (See Appendix C).

4.2.1.2. Post-HCT evaluations

1. CBC at least twice a week from Day 0 until ANC > 500/mm^3 for 2 days after nadir reached. Thereafter CBC twice per week until Day 28 (or 4 weeks), then at 8 weeks, Day 100, 6 months, one year and two years post-HCT.
2. Toxicity assessments at 4 weeks, 8 weeks, Day 100, 6 months, one year and two years post-HCT.
3. Mucositis assessment twice a week until Day 21 using the modified oral mucositis assessment scale (OMAS).
4. Disease restaging:
   a. CT scan at 100 days, 6 months and one year post-transplant
   b. PET or PET CT at 100 days post-transplant, with a 6 month PET or PET-CT performed if the Day 100 scan results are equivocal
5. Evaluation of immune reconstitution by flow cytometry and quantitative immunoglobulins (IgM, IgG and IgA) at Day 60, 180 and one year post-HCT. *Note: Flow cytometry will be performed at project laboratory (See Appendix C) and quantitative immunoglobulins will be performed at the clinical center.*
6. CMV PCR or antigenemia assay measured weekly Day 0 through 8 weeks; follow-up at Day 100.
7. Diagnostic lymphoma pathology specimens (paraffin blocks or 10 unstained slides) sent to the AIDS Cancer and Specimen Resource/AIDS Malignancy Consortium Pathology Laboratory central laboratory within 4 weeks post transplant (See Appendix C).
8. HIV viral copy number, performed at the clinical centers at 100 days, 6 months, 1 year, 2 years by standard clinical assay.
9. For those patients with no detectable viral RNA in their **baseline** sample using the standard clinical test performed at the clinical site, additional post-transplant blood samples will be collected at Day 180, 365 and 730 (See Appendix C).
10. Blood DNA (EBV and Ig DNA) assessments at 100 days, 6 months, and 1 year.
11. Microbial Translocation Monitoring at Days 7, 14 and 100.

TABLE 4.2.1.2A: PRE-ASCT EVALUATIONS

	Prior to initiation of BEAM					
Required Studies/Testing	**3 months**	**8 weeks**	**4 weeks**	**1-3 weeks**	**1 week**	**Day -3 of Conditioning**
CMV IgG, Hepatitis Panel (HAV Ab, HBsAg, HbcAb, HbsAb, HCV Ab), HSV ½ IgG, toxoplasma IgG, VZV IgG, Syphilis (RPR or VDRL) , HIV and HTLV antibody	X					
EKG	X					
PET or PET-CT	X					
DLCO, FEV1, FVC	X					
Creatinine Clearance	X [1]					
CMV PCR or antigenemia assay	X					
Bone marrow biopsy for pathology	X					
HIV RNA, CD4 Count	X					
HepB DNA PCR and HepC DNA PCR are required only if the core Ab are positive	X					
Ejection Fraction	X					
History, Physical Examination, Height and Weight, body surface area, neurologic examination, careful measurement of all palpable peripheral lymph nodes and measurement of other sites of disease present on physical.		X[2]				
β –HCG Serum Pregnancy Test for Females of Childbearing Potential		X				
Quantitative Immunoglobulins (IgM, IgG, and IgA)				X		
CT			X[3]			
Karnofsky Performance Score			X		X	
CBC with differential, Platelet Count, Creatinine, Bilirubin, Alkaline Phosphatase, AST, ALT, LDH, Sodium, Magnesium, Potassium, Chloride and CO_2			X		X	
Central Pathology Review	X[4]					
Plasma DNA Tumor Monitoring (Ig and EBV)					X	X
Microbial Translocation Monitoring					X	X
HIV Single Copy PCR Assessment				X[5]	X[5]	
Optional Future Research Blood Sample				X		

Notes for Table 4.2.1.2A are on the next page.

Notes for Table 4.2.1.2A

[1] Calculated creatinine clearance is permitted.

[2] To include:

a. Lumbar puncture(s) for determination of presence of CNS disease for non-Hodgkin's lymphoma patients only.
b. Duration of AIDS diagnosis, history of prior opportunistic illnesses.
c. Presence or absence of "B"-symptoms (unexplained fevers, night sweats, involuntary weight loss greater than 10% normal body weight).
d. Medication list to include all antiviral, antibiotics and opportunistic prophylaxis.

[3] CT scans of neck, chest, abdomen and pelvis. Neck CT only required if previous site of disease.

[4] Tissue block is preferred but 10 unstained slides may be used as an alternative. Pre-enrollment samples collected during the enrollment evaluation process should be saved, but will only be shipped to Central Pathology Laboratory for review on those patients enrolled onto the study **(**See Appendix C).

[5] Collection of additional blood for HIV single copy PCR assessments will be required for only those patients with undetectable **baseline** HIV viral levels by conventional assay (See Appendix C).

TABLE 4.2.1.2B: POST-HCT EVALUATIONS

Study Assessments/ Testing	Weeks Post-HCT									Months Post-HCT		
	1	2	3	4	5	6	7	8	Day 100	6	12	24
CBC[1]	X[1]							X	X	X	X	X
Toxicity Assessment				X				X	X	X	X	X
Mucositis Assessment[2]	X	X	X									
CT									X	X	X	
PET or PET-CT									X	X[3]		
Immune Reconstitution Assays[4]								X		X	X	
CMV PCR or Antigenemia[5]	X	X	X	X	X	X	X	X	X			
Diagnostic Lymphoma Pathology[6]				X								
HIV Titer by Standard Assay									X	X	X	X
HIV Single Copy PCR Assessment[7]										X	X	X
Microbial Translocation Monitoring	X	X							X			
Plasma DNA Tumor Monitoring (Ig and EBV)									X	X	X	

Notes for Table 4.2.1.2B on the next page

Notes for Table 4.2.1.2B

[1] To be performed at least twice weekly from Day 0 until ANC > 500/mm^3 for 2 days after nadir reached. Thereafter, twice weekly until Day 28 (or 4 weeks), then at 8 weeks, Day 100, 6 months, one year and two years post-ASCT.

[2] To be performed twice weekly until Day 21 using the modified oral mucositis assessment scale (OMAS)

[3] 6 month scan performed if the Day 100 scan results are equivocal

[4] Immune reconstitution assays by flow cytometry and quantitative immunoglobulins (IgM, IgG and IgA). Flow cytometry will be performed at project laboratory (See Appendix C) and quantitative immunoglobulins will be performed at clinical center

[5] CMV PCR or antigenemia assay measured weekly Day 0 through 8 weeks; follow-up at Day 100.

[6] Diagnostic lymphoma pathology specimens (paraffin blocks or 10 unstained samples) collected pre-enrollment should be sent to the AIDS Cancer and Specimen Resource/AIDS Malignancy Consortium Pathology Central Laboratory within 4 weeks of transplant.

[7] Collection of additional blood for HIV single copy PCR assessments will be required for only those patients with undetectable **baseline** HIV viral levels by conventional assay (See Appendix C).

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Overview

This study is designed as a Phase II multi-center trial to assess the overall survival after autologous hematopoietic stem cell transplantation (HCT) for chemotherapy-sensitive aggressive B cell lymphoma or Hodgkin's lymphoma in patients with HIV using BEAM for pre-transplant conditioning. The target enrollment is 40 patients.

5.1.1. Accrual

Accrual will be across multiple sites and remain open until 40 patients are transplanted. It is estimated that two years of accrual will be necessary to enroll the targeted sample size.

5.1.2. Primary Endpoint

The primary endpoint for the study is overall survival. Time-to-event is measured from transplantation to the minimum of the date of death or last follow-up. If any patients are lost to follow-up, they will be censored at the time of the last observation. The study will remain open until the last patient enrolled has been followed for two years.

5.2. Sample Size Calculations

The sample size is 40 patients for this trial. Ninety-five percent confidence intervals were calculated for varying probabilities based on the sample size. Table 5.2 provides confidence intervals for a variety of true underlying proportions. Of particular interest is where the OS probability is 50%, which is the targeted one-year survival probability. For this setting, the confidence interval length is 32.4%. The percentage above and below 50% are meant to represent other plausible survival rates.

TABLE 5.2 POSSIBLE 95% CONFIDENCE INTERVAL FOR VARIOUS UNDERLYING OVERALL SURVIVAL RATES WITH N=40

Overall Survival Rate (%)	Possible 95% Confidence Intervals (%)		Length of 95% Confidence Interval
80	64.4	91.0	26.6
75	58.8	87.3	28.5
70	53.5	83.4	29.9
65	48.3	79.4	31.1
60	43.3	75.1	31.8
55	38.5	70.7	32.2
50	33.8	66.2	32.4
45	29.3	61.5	32.2
40	24.9	56.7	31.8
35	20.6	51.7	31.1
30	16.6	46.5	29.9

The OS probability estimate will be based on the Kaplan-Meier product limit estimator. In the absence of censoring, the Kaplan-Meier estimate reduces to the binomial proportion.

5.3. Interim Analysis and Stopping Guidelines

There will be no interim analyses for efficacy. Monitoring of a key safety endpoint (treatment-related mortality (TRM)) will be conducted at Day 30 and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guidelines serve as a trigger for consultation with DSMB for additional review, and are not formal "stopping rules" that would mandate automatic closure of study enrollment.

The rate of TRM will be monitored up to 30 days post-transplant. A truncated Sequential Probability Ratio Test (SPRT) based on a binomial test of proportions for treatment-related mortality will be used as described below. This sequential testing procedure conserves type I error across all of the monitoring looks for TRM. The SPRT can be represented graphically. At each interim analysis, the number of patients enrolled is plotted against the total number of patients who have experienced TRM. The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring to protect against excessive TRM. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more TRM than predicted by the number of patients on study. Otherwise, the SPRT continues until enrollment reaches the target goal.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. Note that since the test uses only the upper boundary, and is truncated by a finite sample size, the size of the test will be slightly lower than the nominal level. The test to be used in this protocol was developed from the following SPRT:

- An SPRT contrasting 5% versus 15% TRM, with nominal type I and II errors of 9% and 20%, respectively.
- The slope of the parallel lines for monitoring TRM is 0.092 and the intercepts are –1.252 and 1.806.

The stopping rule is summarized in Table 5.3A.

TABLE 5.3A STOPPING GUIDELINES FOR 30-DAY TRM AMONG PATIENTS ENROLLED

Number of patients enrolled	Stopping boundary
3-12	3
13-23	4
24-34	5
35-40	6

* Stopping guideline is triggered if >= x patients out of n patients enrolled experience TRM.

The actual operating characteristics of the truncated test, shown in Table 5.3B, were determined in a simulation study. The simulation assumed uniform accrual of 40 patients over a two-year time period.

TABLE 5.3B OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FOR 30-DAY TRM FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

Treatment-related Mortality				
True 30-day rate	5%	10%	15%	20%
Probability reject the null hypothesis	0.047	0.332	0.683	0.885
Mean month stopped	24.4	21.0	16.0	12.0
Mean # endpoints	1.9	3.4	3.8	3.7
Mean patients with 30 days follow-up	39.0	33.4	25.4	18.9

Treatment-related mortality is monitored in all patients. The SPRT rejects the null hypothesis in favor of the alternative 5% of the time when the true 30-day TRM is 5%, and 88% of the time when the true 30-day TRM is 20%. This corresponds to a type I error rate of α=0.05 and a type II error rate of β=0.12. When the true 30-day TRM rate is 20%, on average, the DSMB will be consulted 12 months after opening, when 3.7 events have been observed in 18.9 patients**.** Note

that the SPRT procedure is adequately powered to distinguish between a TRM rate of 5% and 20%.

5.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, disease stage, genotype, HIV load, CD4 counts, and number of prior chemotherapy regimens as treatment of primary malignancy and number of prior HIV regimens.

5.5. Analysis Plan

5.5.1. Analysis of the Primary Endpoint

The primary analysis will consist of estimating the 1 year OS probability from the time of transplantation based on the Kaplan-Meier product limit estimator. The 1 year OS and confidence interval will be calculated.

5.5.2. Analysis of Secondary Endpoints

Time to Progression
The event is relapse/progression. Death without relapse/progression is considered a competing risk. Patients alive with no history of relapse/progression are censored at the time of the last observation. Time-to-relapse or progression will be measured from transplant. A cumulative incidence curve will be computed along with a 95% confidence interval.

Progression-Free Survival (PFS)
The event is relapse/progression or death. The time to this event is the time from enrollment until death, relapse/progression, receipt of anti-lymphoma therapy, or last follow up, whichever comes first. Progression-free survival (PFS) will be estimated using the Kaplan Meier product limit estimator. The PFS probability and confidence interval will be calculated at one and two years post-transplant.

CR and CR+PR Proportion at Day 100
The frequencies and proportions of patients who have a CR (or PR) will be described with confidence intervals at Day 100.

Time to Progression after CR
The event is relapse/progression after complete response. Death after CR without relapse/progression is considered a competing risk. Patients who achieved CR and alive with no history of relapse/progression are censored at the time of the last observation. Time-to-relapse or progression will be measured from documentation of complete response for patients entering the trial in PR and from enrollment for patients entering the trial in CR. A cumulative incidence curve will be computed.

Lymphoma Disease-Free Survival
The event is death or relapse after complete response. The time to this event is the time to relapse, death or last follow-up, whichever comes first, measured from documentation of complete response for patients entering the trial in PR and from enrollment for patients entering the trial in CR. Lymphoma Disease-Free survival will be estimated using the Kaplan Meier product limit estimator.

Time to Hematopoietic Recovery
Time to neutrophil recovery and platelet engraftment will be estimated using cumulative incidence function with death prior to engraftment as the competing risk.

Hematologic Function
The proportions of patients with hematologic function at Day 100 and 1 year will be described with confidence intervals in patients surviving to these time points.

Toxicities
Toxicities that occur over the course of time will be tabulated using the version 3.0 CTC AE criteria. The proportion of patients developing toxicity will be described by type of toxicity, grade, and time period.

Incidence of Infections
Microbiologically documented infections will be reported by site of disease, date of onset, severity, and resolution, if any, up to two years post-transplant.

Treatment-related Mortality
Treatment-related mortality (TRM) is defined as death occurring in a patient from causes other than relapse or progression. A cumulative incidence curve will be computed along with a 95% confidence interval at 100 days post-transplant.

Immunologic Reconstitution
Immune reconstitution assays on peripheral blood, which include (i) immunophenotypic analysis of both T and natural killer subsets; (ii) functional evaluation of adaptive and innate immune responsiveness; and (iii) quantitative immunoglobulin measurement (IgM, IgG and IgA). Studies will be performed at Days 60, 180, and 1 year post-transplant. These will be summarized at each time point using descriptive statistics.

HIV Reservoir
HIV RNA assay prior to transplant and at Day 100, 180 and 1 year post transplant (for HIV load) will be performed. For patients with no detectable viral RNA using the standard clinical test, a single copy assay will be used to measure the viral reservoir. We will summarize this assessment of the viral copy number using descriptive statistics at each time point, and we will investigate changes in the viral copy number from pre-transplant to post-transplant time points using Friedman's nonparametric test.

Microbial Translocation

Association between outcome (hyperbilirubinemia, VOD, and death) at Day 30 and Day 100 post transplant and level of microbial translocation markers will be determined by nonparametric Mann-Whitney tests comparing the distribution of prior microbial translocation markers between patients with vs. without each outcome.

Blood DNA

Plasma DNA (clonal Ig, EBV) and PBMC EBV DNA measured within 1 week of initiation of conditioning, on Day -3 of conditioning, at Day +100, 6 months and 1 year post-transplant will be summarized using descriptive statistics.

The probability of patients relapsing or progressing by one or two years post-transplant will be estimated using the cumulative incidence function separately for patients with vs. without the presence of plasma DNA at each measured time points (both pre- and post-transplant). For plasma DNA measured post-transplant, the analysis will be restricted to patients who are alive and have not yet relapsed/progressed by the time of plasma DNA measurement. The association between the presence of plasma DNA at each time point and subsequent progression/relapse at one or two years will be determined by the Chi-square test.

APPENDIX A

HUMAN SUBJECTS

APPENDIX A

HUMAN SUBJECTS

1. Subject Consent

A conference will be held with the patient and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The Principal Investigator or another designated physician will conduct the conference. All potential risks associated with BEAM and HSCT or should be discussed as objectively as possible.

The consent document should be reviewed with the patient and family prior to proceeding to ablative therapy.

Informed consent from the patient will be obtained using a form approved by the Institutional Review Board of the institution enrolling the patient.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the BMT CTN Data Coordinating Center upon enrollment.

3. Participation of Women and Minorities and Other Populations

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of DLCL in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

APPENDIX B

CONSENT FORMS

Informed Consent to Participate in Research

Principal Investigator Contact Information
(Insert contact information for PI at your site)

Study Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Introduction
This is a clinical trial, which is a research study to answer specific medical questions. The information from this study will help future patients. The Study doctor (the person in charge of the research) will explain the clinical trial to you. Clinical trials include only people who choose to join the study.

Please take your time to decide if you want to join this study. Some people find it helpful to talk about the study with their family and friends before they make a decision. It may also be useful to talk with your doctor and other people on your health care team about the study. If you have questions or want to know more about the study, you can ask them for more information.

You are being asked to take part in this study because you have an HIV related chemotherapy-sensitive aggressive B cell lymphoma or Hodgkin's lymphoma which has either not fully responded to the initial treatment or has returned. An autologous peripheral blood stem cell transplant is when your own stem cells are collected from your blood, frozen, and then given back to you after you receive chemotherapy, also referred to as conditioning therapy.

Why is this study being done?
This approach is fairly standard for patients with lymphoma. However, in patients with HIV, there are some special issues. This study is being carried out to better define the risks and benefits of this approach to therapy in HIV patients. Results of this trial will help guide treatment decisions for future HIV patients.

How many people will take part in the study?
Forty patients will take part in this study.

What will happen if I take part in this research study?
Before you begin the study **--** You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. The tests include:

- Medical history
- Physical examination, including height and weight
- Blood and urine tests
- EKG
- Heart function tests
- Pulmonary (lung) function tests
- Tests to evaluate your lymphoma including PET/CT scans and a bone marrow biopsy
- A blood pregnancy test if you are a woman able to have children; if you are pregnant, you will not be able to take part in this study.

During the study *(you can refer to the Study Chart later in this consent as you read this)* **–**

Antiretorviral Therapy
Antiretroviral therapy will be stopped before transplant chemotherapy begins and will not be reinitiated until the WBC has recovered. This is done for two reasons. It is common for the chemotherapy to cause nausea and vomiting that would interrupt antiretroviral therapy. We believe repeated interruptions are more dangerous than a planned stop and then restart after nausea has resolved. In addition, some antiretroviral therapies may have effects on the bone marrow during its recovery (zidovudine) or may interact with chemotherapy drugs so as to lead to increased or unpredictable toxicities. Patients who were on zidovudine prior to transplant will be started on an alternative antiretroviral in place of zidovudine.

Conditioning Regimen
The conditioning regimen is used to kill the lymphoma cells in your body. BEAM is the pre-transplant conditioning regimen you will receive. You will receive BEAM chemotherapy starting 6 days before your transplant. BEAM is a very common combination of chemotherapy drugs that has been widely used in transplants for Lymphomas.

Reinfusion of Stem Cells (Transplantation)
After the conditioning regimen, the stem cells that were previously collected and frozen will be thawed and reinfused into you through your catheter. You will then receive the autologous cells that were collected and frozen during mobilization (this day that you receive your cells is referred to as Day 0). The cells will travel to your bone marrow where they'll begin making healthy, new blood cells. This step is necessary because the high dosages of chemotherapy given to you during the conditioning regimen will not only destroy lymphoma cells, but healthy cells in your bone marrow as well. Until the new stem cells begin producing healthy blood cells, you will be at an increased risk of excessive bleeding or developing an infection.

Description of Study Drugs

BEAM- BEAM is a mixture of several chemotherapy drugs that interfere with the growth of cancer cells and are widely used to treat NHL:

BCNU (also called carmustine)

Etoposide (also called VP-16)

Ara-C (also called cytarabine)

Melphalan

When you are finished taking these drugs and have received your transplant, you will be watched closely. For this study, you will have the following tests at least twice per week for the first 4 weeks and then again at 8 weeks, 100 days, six months, one year and two years after transplantation:

- Medical history
- Physical examination
- Blood and urine tests

In addition to these tests, you will have blood drawn to test how well your immune system is working before you begin treatment and at 60 days, six months and one year after your transplant.

Tests and exams to look at the status of your lymphoma will be done 100 days, 6 months, 1 year and 2 years after your transplant. These will include PET and CT scans.

All of these exams, tests or procedures are part of regular medical care after a transplant and may be done even if you do not join the study. The schedule for testing is only for tests required for the study. Some of these tests will be done more frequently than described here if your doctor thinks it is necessary for your medical care.

How long will I be on this study?
After your transplant, the study doctor will ask you to visit the office for follow-up exams for two years to receive the study tests and procedures described above.

Follow up for your transplant will last as long as you require care. However, we would like to keep track of your medical condition for the rest of your life by contacting you and the doctor providing your regular medical care by phone or mail once a year. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study and transplantation in general. Many transplant centers include this type of long-term follow-up as part of their regular medical care. It is not necessary for you to agree to follow-up for longer than 5 years to participate in this study.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your doctor if you are thinking about stopping so any risks from the medications can be evaluated. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Can the Study Doctor withdraw me from the study?
You can be taken off the study (with or without your consent) for any of the following reasons:

- You do not qualify to be in the study because you do not meet the study requirements. Ask your doctor if you would like more information about this.
- You need a medical treatment not allowed in this study.
- The study doctor decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant.
- You are unable to keep appointments or take study drugs as directed.
- Other study-specific reasons; for example, if the dose of study drug you are taking is found to be unsafe.
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH).

What side effects or risks can I expect from being in the study?
You will have side effects while on the study. Side effects may be mild or very serious. Your health care team will give you medicines to help lessen side effects such as nausea. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death. Most of these risks are common to all patients undergoing autologous transplant but some, such as risk of infection or organ damage may be different in patients with HIV.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Potential Side Effects

BEAM		
Likely	**Less Likely**	**Rare but Serious**
• Low blood counts • Nausea/vomiting • Mouth sores • Sores in esophagus • Abdominal pain/diarrhea • Difficulty eating • Hair loss • Fatigue	• Liver problems • Lung problems • Low blood pressure • High levels of uric acid • Skin rash • Chills	• Liver failure • Severe lung problems • Severe allergic reactions • Second cancers, including Myelodysplastic Syndromes (MDS) and leukemia • Life-threatening infection • Disease of the peripheral nervous system • Sterility

Reproductive Risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future.

This study is designed to help persons who are suffering from lymphoma. However, this treatment may not cure your lymphoma. We do not expect that this treatment will have any long term effect on the course of your HIV infection.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. We do know that the information from this study will help doctors learn more about transplantation for lymphoma in HIV patients. This information could help future HIV patients with lymphoma.

What other choices do I have if I do not take part in the study?
Your other choices may include:

- Treatment with other drugs or a combination of drugs without a transplant.
- An autologous stem cell transplant that is not part of the study or another type of transplant.
- No therapy directed against your lymphoma at this time.

Talk to your doctor about your treatment choices before you decide if you will take part in this study.

What are the costs of taking part in this study?
You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

All costs of your care including the chemotherapy drugs and costs associated with administration of them will need to be paid by you and/or your health plan/insurance company. All of the medical tests, evaluations and procedures in this study are considered part of standard medical care.

The companies that make the drugs used in this study did not plan or design this clinical trial. They will also not have a part in analyzing the results of this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?
It is important that you tell your doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Will my medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research, organizations involved in research on blood and marrow transplantation and in the coordination of this study
- The EMMES Corporation, a research organization that is helping to coordinate this study
- Members of the Blood and Marrow Transplant Clinical Trials Network, which is conducting this study
- The National Heart, Lung, and Blood Institute (NHLBI), the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

HIPAA[1] authorization to use and disclose individual health information for research purposes

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *High Dose Chemotherapy with Autologous Stem*

1 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

Cell Rescue for Aggressive B Cell Lymphoma and Hodgkin Lymphoma in HIV-infected Patients.

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results).

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:

(list hospitals, clinics or providers from which health care information can be requested)

_____

_____

_____

d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Members of the BMT CTN Data and Coordinating Center and 0803 Protocol Team
- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
- Other:

_____

_____

_____

e. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my

decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____*[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

You will get a copy of this form. If you want more information about this study, ask your study doctor.

****

About Using Blood for Research

Please note: This section of the informed consent form is about future research studies that will be done using blood samples from people who are taking part in the main study described above. You may give small blood samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to giving blood samples for future research studies. You can say "yes" or "no" to giving blood samples for future research studies. Please mark your choice at the end of this section.

We would like to have one small (4 teaspoons or 20 mL) blood sample for future research. If you agree, this sample will be obtained pre-transplant. They will be kept and may be used in research to learn more about HIV, cancer and other diseases. Usually the blood can be drawn from your central venous catheter at the time of the other blood collections. If this is not possible, it will be taken from a vein. When the sample is given to investigators for research, no information about your name, address, phone number or other information that will let the researcher know who you are will be provided.

The samples collected for research purposes will be sent to the AIDS and Cancer Specimen Resource Repository. The samples will be labeled with unique codes that do not contain

information that could identify you. A link to this code does exist. The link is stored at the Data and Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the repository where your sample is being stored does not have a link to this code. Your research samples will continue to be stored at the ACSR Repository until they are used up for approved research.

DNA from your stored blood and tissue samples and your health information might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH).

Genome-wide association studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease.

If your coded genetic and clinical information is used in such a study, the researcher is required to add the DNA test results and non-identifying information into a public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

The research that may be done with your blood is not designed specifically to help you. It might help people who have HIV, cancer and other diseases in the future.

Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About: The choice to let us have blood samples for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.

In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the researchers reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.

Benefits: The benefits of research using blood include learning more about what causes HIV, cancer and other diseases, how to prevent them, and how to treat them.

Risks: The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice: Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

Statement of consent

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood and information can be stored indefinitely by the BMT CTN and/or AIDS and Cancer Specimen Resource Repository for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

- ❑ Yes, I agree to have a blood sample drawn for future research.
- ❑ No, I do not agree to have a blood sample drawn for future research.

_____ _____

Signature *Date*

****

SIGNATURE

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Witness _____

Date_____

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

_____
Signature of person conducting informed consent

Date_____

ASSENT FORM

High Dose Chemotherapy with Autologous Stem Cell Rescue for Aggressive B Cell Lymphoma and Hodgkin Lymphoma in HIV-infected Patients

A. Why am I here?

We are inviting you to join our study because your first treatment for your lymphoma did not work or your lymphoma has come back, and because you have HIV.

B. Why are you doing this study?

We want to know how well autologous transplant treats lymphoma in people with HIV.

C. What will happen to me?

If you say you want to be in the study, we will ask you for several things:

- Permission to let us read your medical records and x-rays.
- Participate in getting tests done to find out more about your health.
- Check-ups with the study doctors for at least two years.
- Some blood from you (about 12 teaspoons). A very small needle will be used to get blood.

For this study, you will have an autologous transplant.

What is an autologous transplant?

An autologous transplant uses stem cells collected from your blood stream or bone marrow to rebuild your immune system. There are three main steps to this type of transplant. First, we will give you a series of four drugs (chemotherapy) to destroy your unhealthy cells (lymphoma) in your blood steam and bone marrow. Second, we will collect the rest of your cells from your blood stream or bone marrow, treat them and store them. Third, we will give you back your treated cells that, after a brief delay, will make new, healthy cells.

During and after your transplant, we will watch you carefully for fevers, any sign of infection or other problems. You may have to stay in the hospital. You may require daily visits to a clinic during your transplant. Once your transplant is complete, you will need to come back for regular visits and testing for at least 2 years for this study. Your doctor may want to see you for longer than 2 years.

D. Will it hurt?

You will get sick from the chemotherapy. Side effects of these drugs include nausea and vomiting, mouth sores, stomach pain, skin rash, and lowering of your blood counts. We will give you drugs to treat most of these side effects. One side effect, which we cannot prevent, will be hair loss. This will occur about 2-3 weeks after you receive the medicines. This is only temporary.

When you have your blood and cells taken with a needle, it may feel like a pinch. It will hurt for a minute and sometimes the place where the needle went might be red and sore. You might get a little bruise where the blood was taken but it goes away in a few days.

A stem cell transplant requires us to give you many drugs through your vein, and to sample your blood many times. To make this easier for you, we will place a tube in your neck or chest. We will give drugs before the tube is placed in to make you sleepy, so you won't feel it going in. Once this tube is place, you will not need any more needle sticks. When the transplant is done and you are feeling well, the tube will be removed.

E. Will the study help me?

We don't know if the study will help you or not. Your lymphoma may stay the same, it may get better, or it may get worse. It is not known if the study will help your HIV.

F. What if I have questions?

You can ask any questions that you have about the study. If you forget to ask a question and think of it later, you can call me [insert office number]. You can also ask your question the next time you see me.

You can call the study office at any time to ask questions about the study.

G. Do I have to be in this study?

- If you don't want to be in the study, you need to tell us and your parent or guardian. Your doctor will not be angry or upset if you don't want to join.
- Whether you are in the study or not, you will still need to have treatment for your lymphoma.
- You can say yes now and change your mind at any time.
- Please talk this over with your parent or guardian, and other family members, before you decide if you want to be in the study. We will also ask your parents to give their permission for you to join this study.

Writing your name on this page means that you agree to be in the study, and know what will happen to you. If you decide to quit the study, all you have to do is tell the person in charge.

You and your parent or guardian will get a copy of this form after you sign it.

Signature of Child	Date
Signature of Researcher	Date

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

1. CHARACTERIZATION OF THE RATES, SPECTRUM, RISK FACTORS, AND OUTCOMES OF INFECTIONS

HCT-related risk factors for infection (time to engraftment, degree of mucositis, duration of neutropenia) and HIV-related (CD4, VL, HAART resistance) risk factors will be investigated. Specimens will be collected to allow the analysis of the relationship of microbial translocation markers to febrile neutropenia and infectious outcomes.

Background
Recent observations that persons with chronic HIV-1 infection and AIDS demonstrate increased microbial translocation (MT) from the gut compared to uninfected persons may be related to the massive depletion of intestinal CD4+ lymphocytes within weeks of HIV-1 acquisition (1). Our group also recently demonstrated that microbial translocation in HIV-HCV co-infection was strongly associated with more rapid progression of liver cirrhosis. A key finding was that serum endotoxin (LPS) level, a marker of microbial translocation, was higher in patients with more advanced fibrosis (2). The detection of microbial translocation in peripheral blood likely underestimates the higher quantities of microbial products that enter the portal venous circulation with resulting sequelae in the liver.

Previous studies have shown that HIV+ recipients of autologous stem cell transplant are at risk for early hepatic veno-occlusive disease (VOD) (3). VOD is a condition which is characterized by endothelial cell injury in the hepatic sinusoids leading to sinusoidal thrombosis and occlusion. LPS is known to have a procoagulant effect by inducing gene expression of several inflammatory mediators including the procoagulant protein, tissue factor (4). Therefore, a high level of circulating MT markers (such as LPS) at the time of transplant could be a risk factor for development of early hepatic VOD. Moreover, monitoring serum levels temporally to explore associations with liver associated morbidity including VOD, may provide insights into defining risk factors for VOD. The long term goal of this approach is to provide a rational basis for targeted antimicrobial therapy to reduce microbial translocation in patients at higher risk of developing VOD.

Hypothesis
We hypothesize that increased microbial translocation in HIV infected recipients of induction chemotherapy may increase the risk for development of veno occlusive disease after autologous or allogeneic stem cell transplant.

Study Objectives
We propose testing archived sera for microbial translocation markers from HIV-infected persons who have received autologous stem cell transplant. Microbial translocation marker levels will then be correlated with clinical outcome (hyperbilirubinemia, development of VOD, death) as patients are followed longitudinally.

Study Design
Clinical data that will be obtained at baseline will include age, gender, race, HCV RNA levels, HIV RNA levels, CD4+ lymphocyte count, AST, ALT, total bilirubin, antibiotic usage within the prior 6 weeks, antiretroviral therapy, MELD score, and a history of liver-related complications.

Microbial Translocation Measurements
Markers of microbial translocation that will be tested include plasma LPS, LPS-binding protein (LBP), soluble CD14 (sCD14), and the polyclonal IgM antibody directed toward the LPS core polysaccharide (EndoCAb IgM). LPS testing will be done using the *Limulus* Amebocyte Lysate (LAL) assay (Lonza), while LBP (Cell Sciences), sCD14 (R&D Systems), and EndoCAb IgM (Hycult Biotechnology) assays are all standard plate-based ELISA tests. Microbial translocation markers will be log-transformed to normalize the data, as has been done previously. Values of the LAL assay < 10 pg/mL are considered below the linear range of the assay and will be considered 5 pg/mL (mean of 0 and 10 pg/mL) for standard calculations.

Statistical Components
Association between outcome (hyperbilirubinemia, VOD, and death) at Days 7, 14 and 100 post transplant and level of microbial translocation markers will be determined by nonparametric Mann-Whitney tests comparing the distribution of prior microbial translocation markers between patients with vs. without each outcome.

Samples Required

Pre-transplant

A 10 mL peripheral blood sample will be collected in an EDTA containing Vacutainer tube 1 week prior to conditioning as well as on day 3 of ablative chemotherapy.

Post-transplant

A 10 mL peripheral blood sample will be collected in an EDTA containing Vacutainer tube will be collected at Days 7, 14, and 100 post transplant.

Samples Shipment

Transplant centers will ship whole blood tube by priority overnight FedEx on the day of collection to the project laboratory for processing and microbial translocation marker testing.

References

1. J. M. Brenchley et al., *Nature Medicine* 12, 1365-1371 (2006).
2. A. Balagopal et al., *Gastroenterology* 135, 226-233 (2008).
3. T Spitzer et al., *Biol of Blood and Marrow Transpl.* 14, 59-66 (2008).
4. Luyendik et al., *J Immunol.* 180, 4218-4226 (2008).

2. CHARACTERIZATION OF HIV INFECTION IN AIDS RELATED LYMPHOMA

Background and Rationale
The effect of marrow ablative chemotherapy on the HIV reservoir is not known, but the model of ARL treatment does provide an opportunity to define changes which are associated with HCT. In the current study, we propose to characterize the HIV infection during and after such lymphoma treatment, by measurement of HIV load including the use of an assay which measures HIV at less than 1 copy per milliliter. In patients with no detectable viral load by standard clinical assays, this assay regularly detects low copy number viral RNA. This RNA is believed to be released from latency compartments established in hematopoietic cells.

Hypothesis
We hypothesize that treatment of ARL using dose-intense cytotoxic therapy in patients will result in a substantial reduction in the size of the HIV reservoirs and thus in this very low level viremia. This study will represent the first application of this single copy PCR technique to high dose therapy with autologous hematopoietic stem cell transplant—although the approach has been used multi-institutional studies of anti-retroviral therapies.

HIV Single-Copy HIV Viral Titer Measurements
In patients with undetectable viral load as measured in conventional assays, there is persistent viremia that can be measured at single copy/ml by specialized PCR analysis. This viremia may reflect virus being released by the decay of latently infected cells or possibly ongoing viral replication. Therapies that impact on the latently infected reservoir might be expected to change the viremia if it mainly reflected the decay of latently infected cells. Myeloablative chemotherapy may kill cells that constitute the latency reservoir and thus might thus be expected to impact on the reservoir and the very low level viremia that can be assessed by this assay.

Samples Required

Pre-transplant

A 20 mL peripheral blood sample will be collected in EDTA containing Vacutainer tubes 1-3 weeks and 1 week prior to initiation of ablative therapy.

Samples collected only on patients with negative pre-transplant baseline HIV titer by standard assay.

Post-transplant

A 20 mL peripheral blood sample will be collected in EDTA containing Vacutainer tubes on Days 180, 365, 730 post-transplant.
Samples collected only on patients with negative pre-transplant baseline HIV titer by standard assay.

Sample Processing and Shipment
Transplant centers will process plasma sample, snap freeze, and ship frozen twice a year by priority overnight FedEx on the day of collection to the project laboratory for testing. See BMT CTN 0803 Laboratory Sample Guide for detailed procedure for specimen processing.

3. CHARACTERIZATION OF THE UTILITY OF PLASMA DNA MARKERS FOR AIDS LYMPHOMA

Background
As the safety of HIV auto transplants have gained acceptance, new questions have emerged with regard to aspects of HIV biology, HIV lymphoma tumor markers, and the relationship between gut and liver dysfunction that can be uniquely addressed in the context of a trial involving high dose myeloablative chemotherapy.

Plasma DNA
Tumor DNA detected in plasma is emerging as a potentially useful tumor marker. Two candidate tumor markers in patients with HIV lymphomas have emerged. These are i) clonal Ig DNA as recognized by Ig rearrangements or characteristic somatic hypermutation and ii) EBV DNA. In a small series, clonal Ig DNA is characteristic of a particular patient's B cell tumor and is detected in approximately half of AIDS diffuse large B cell lymphoma prior to treatment. In that series, patients in whom clonal Ig DNA persists in plasma inevitably relapse. EBV DNA detected in plasma is useful as a tumor marker in nasopharyngeal carcinoma where evidence suggests that viral genomes are released from apoptotic tumor cells rather than being present as virions. In AIDS, high copy numbers of EBV genomes is present in many HIV patients and in studies from the Multi-Center AIDS Cohort Study, have demonstrated very modest value to EBV determinations. Recent evidence suggest that tumor cell derived viral DNA may be distinguished from virion DNA because virion DNA is not CpG methylated. Thus meCpG EBV DNA may specifically mark tumor DNA.

Plasma DNA (clonal Ig, methyl EBV) measured prior to conditioning, prior to stem cell infusion, and at Day +100, 6 months and 1 year post-transplant will be summarized using descriptive statistics.

The probability of patients relapsing or progressing by one or two years post transplant will be estimated using the cumulative incidence function separately for patients with vs. without the presence of plasma DNA at each measured time points (both pre and post transplant). For plasma DNA measured post transplant, the analysis will be restricted to patients who are alive and have not yet relapsed/progressed by the time of plasma DNA measurement. The association between the presence of plasma DNA at each time point and subsequent progression/relapse at one or two years will be determined by the Chi-square test.

Samples Required

Pre-transplant

A 10 mL peripheral blood sample will be collected in an EDTA containing Vacutainer tube within 1 week prior to initiation of ablative therapy.

A 10 mL peripheral blood sample will be collected in an EDTA containing Vacutainer tube on Day -3 of conditioning..

Post-transplant

A 10 mL peripheral blood sample will be collected in an EDTA containing Vacutainer tube will be collected at Days 100, 180, and 365 post-transplant.

Samples Shipment
Transplant centers will ship whole blood tubes by priority overnight FedEx on the day of collection to the project laboratory for processing and testing.

4. IMMUNOPHENOTYPIC AND FUNCTIONAL CHARACTERIZATION OF IMMUNE RECONSITUTION

Background and Rationale:
Little is known about immune reconstitution following autologous stem cell transplantation to treat patients with hematologic malignancies in patients with HIV infection. Multiple variables including adaptive immune dysfunction and chronic viral infections raise the possibility that HIV+ patients will encounter more infectious complications compared to HIV- individuals following stem cell transplantation. It will therefore, be critical to perform correlative laboratory investigations examining adaptive and innate immune surveillance in this very unique setting. The use of multiparametric flow cytometry to identify specific adaptive and innate immune cell subsets, and use of available pathogen-specific epitopes should allow us to characterize the dynamics of immune reconstitution and identify first responses against HIV and other common pathogens post-ASCT.

Hypothesis:
We hypothesize that quantitative and qualitative differences in adaptive and innate immune reconstitution will correlate with clinical outcome in HIV+ patients who undergo autologous stem cell transplantation. Improved understanding of immune reconstitution in this very unique setting will lead to advances in the management of HIV+ patients with cancer and lead to novel approaches to improve long term survival of these patients.

Study Design:
Immunophenotypic Evaluation of T and NK Cell Subsets: To date no comprehensive muti time point study has been performed to evaluate reconstitution of adaptive immunity in HIV+ patients treated with peripheral blood stem cell transplantation. Examining the nature of adaptive and innate immune reconstitution will involve use of a multi panel flow cytometric assay to track changes in naïve, memory, activated and regulatory T cell subsets. Specifically, these studies will involve a detailed in vivo analysis of early, mid, early-late and late activation

of B and T lymphocytes and characterization of T cell subsets including naïve, memory, Th1, Th2 and T regulatory cells. In addition we will evaluate maturation status of NK cells and their activation status. Multiparametric flow analysis will be performed on fresh peripheral blood samples collected at 60, 180 and 365 days post stem cell infusion.

Table 1 Multicolor T Cell Panel

Condition	FITC	PE	ECD	PC5	PC7
gate purity	CD3	CD56+ CD16	CD19	CD45	CD13
Activation	HLA DR	CD69	CD3	CD134	CD45
Med activation	CD8	CD49a	CD4	CD3	CD45
Naïve/memory cells	CD45RA	CD27	CD45RO	CD4	CD8
Naïve/memory cells	CD45RA	CD29	CD45RO	CD4	CD8
TH1/Th2	CD193	CD294	CD4	CXCR3	CD45
Th1/Th2	CD193	CD294	CD4	CD45	CCR4
T regulatory cells	CD8	CD127	CD4	CD25	CD45
TCR α/β and g/d	TCR $\gamma\delta$	TCR $\alpha\beta$	CD45	CD3	

Table 2 Multicolor NK Cell Panel

Condition	Flow Cytometric 5-color antigen panels				
Viability		7-AAD			
NK cell activation	CD45-PC7	CD3-FITC	CD158-PE	CD69-ECD	CD56+CD16-PC5
NK cell degranulation status	CD45-PC7	LAMP-1 CD107a+ CD107b - FITC	NKG2A CD159-PE	CD3-ECD	CD56+CD16-PC5
NK cell degranulation status	CD45-PC7	LAMP-3 CD63-FITC	NKG2D CD314-PE	CD3-ECD	CD56+CD16-PC5
NK Cell maturity status	CD45-PC7	CD3-FITC	CD16-PE	CD56-ECD	CD117-PC7

Samples of ACD (yellow top) and EDTA (lavender top) anticoagulant containing blood will be received at the project laboratory within 24h following collection and processed immediately upon receipt in the clinical flow cytometry laboratory. Prior to staining, all samples will be analyzed for viability using 7AAD method. Only samples with mononuclear cell viability $\geq$ 90% will be considered acceptable for further analysis. Viability of >95% is achieved in ACD tubes stored at room temperature for up to 48 hours. All samples will be stained using a PrepPlus2 automated staining system (Beckman Coulter) utilizing a five color whole blood staining technique with panels of directly conjugated monoclonal antibodies (see tables 1 and 2) used in quantities that have been predetermined and standardized in our flow cytometric laboratory. Following 30 minutes of incubation at room temperature in the dark, red cells will be lysed using a Q-prep instrument and Coulter Lyse reagent according to manufacturer's recommendations. Samples will be analyzed on FC500 flow cytometer equipped with CXP software version 2.1 (all equipment and reagents by Beckman Coulter). Multiparametric analysis will be performed with a gating strategy based on CD45 staining and light side scatter characteristics that allow adequate separation of lymphocyte, monocyte and myeloid cell populations. Detailed immunophenotypic characterization of the lymphocyte gate will be performed using Prism plot algorithm (Beckman Coulter). The results will be reported as percent of lymphocyte gate and as percent of total leukocytes analyzed. The results will also be reported as an absolute number of specific cell subset types per microliter of whole blood. Absolute cell number will be calculated based on duel platform method using percent of lymphocytes expressing specific immunophenotypic profile (derived from prism plot) and absolute number of lymphocytes derived from analysis of each whole blood sample using ActDIFF hematology analyzer (Beckman Coulter).

Functional Evaluation of Adaptive Immune Reconstitution: We will serially evaluate adaptive cellular immunity by tracking responsiveness to viral recall antigens. We will follow responsiveness to HIV as well as common viral pathogens like CMV and EBV. Studies will use pools of overlapping 15-18mer peptides from full length viral proteins (JPT Technologies) encoded by CMV (pp65), EBV (BZLF1) and HIV (gag). Aliquots of frozen PBMCs will be thawed and enumerated. $1x10^6$ PBMCs will be cultured in the presence of individual viral pooled peptide preparations (or actin control pooled peptides, 1ug/ml final concentration) in the presence or absence of agonistic anti CD28 monoclonal antibody to control for costimulatory signals and provide an optimal condition for evaluation of responsiveness. Following overnight incubation (in presence of brefeldin A golgi plug reagent), a multi color flow cytometric evaluation will identify CD3/CD8 subsets that costain with IFNγ or CD107a (degranulation marker). Separate controls with 7AAD will evaluate PBMC viability. 1×10^5 CD3+ events will be collected using a FC500 flow cytometer and percentage of CD3/CD8+ T cells staining positive for IFNγ and or CD107a will be determined. Outcome of these bioassays will be correlated with immunophenotypic and clinical patient data.

Functional Evaluation of Innate Immune Reconstitution: Innate immune reconstitution studies will examine natural killer (NK) cell responsiveness to cytokines and to FcγRIIIa signaling. NK cell responsiveness assays will be performed on purified NK cells that will be isolated via rosette-sep immuno selection kits. To test cytokine responsiveness, $1x10^5$ NK cells will be incubated overnight in standard culture medium (supplemented with human AB serum) in interleukin 2 (IL-2 10nM) +/- IL-12 (10ng/ml). To evaluate FcγRIIIa responsiveness, 2 methods will be employed: (i) Immobilized IgG in presence or absence of IL12; and (ii) anti FcγRIIIa monoclonal antibody treatment +/- IL12. For FcgRIIIa signaling studies, 96-well flat-bottom plates will be coated with 100 μg/mL huIgG in cold PBS overnight at 4°C, washed with cold PBS, and then plated with immune cells (2×10^5 cells/well) +/- 10 ng/mL IL-12 (or saline control). At 24 and 48 hours cell-free culture supernatants will be harvested and analyzed for levels of IFN-γ by enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN). NK cells will be checked for viability following the overnight pretreatment period and again at the conclusion of the experiment. The readout for the assay will be IFN-γ measured by ELISA or intracellular IFNγ and CD107a expression determined by flow cytometry (as in adaptive immune reconstitution studies) at 24 and 48 hrs. FcγRIIIa responsiveness can also be tested via use of anti FcγRIIIa mAb (clone 3G8) to cross link receptors +/- IL12 and IFNγ and CD107a detected via flow cytometry. Positive controls will include PBMCs collected from immune-competent individuals, purified NK cells from immune-competent individuals incubated with IL2 + IL12, IL-15 + IL-18 and IL-15 + IL-21. We will correlate the outcome of these biologic studies with immunophenotypic studies examining NK cell subsets and clinical patient data.

Quantitative Immunoglobulin Measurement:
Measurement of IgA, IgG, IgM will be performed at individual institutions and data collected periodically. Time points for collection include prior to initiation of conditioning, days 60, , 180 and 1 year post transplantation.

Correlative Evaluation of Immune Reconstitution Studies:
Immunophenotypic and functional immune reconstitution studies will produce quantitative and qualitative data that can be compared to multiple clinical and laboratory outcomes in this unique setting. Specifically:

1) Clinical outcome: Recovery of specific T and NK cell subsets and functional immune responseiveness in the above assays can be compared to (a) documented infections post transplant (bacterial, fungal, viral) CR; (b) lymphoma disease free survival; (c) overall survival.
2) Laboratory comparisons: immunophenotypic and functional immune reconstitution can be compared to the following laboratory correlates: (a) chronic viral infection/reactivation (EBV, CMV, HIV); (b) virion EBV genome copy number (Methylated CpG containing episomes).

Statistical Components:
Immune reconstitution results will be summarized at each post transplant time point using descriptive statistics. Individual T, B and NK cell subsets identified by flow cytometry will be reported as percent of total mononuclear cells and as absolute cell numbers per microliter of peripheral blood. Statistical evaluation of functional studies evaluating adaptive and innate immune reconstitution will be reported as percentage of mononuclear cell subsets staining positive for IFNγ or granzyme B relative to control conditions. Two sided T tests will be employed for evaluation of statistical significance with $p \leq 0.05$ considered significant.

Samples Required:
A total of 37 mL peripheral blood will be collected and placed into (1) four 8.5 mL-fill, ACD Vacutainer tubes (yellow top) tubes containing ACD anticoagulant solution, and (2) one 3 mL EDTA containing (lavender) Vacutainer tubeSample shipment Transplant centers will ship whole blood tubes by priority overnight FedEx on the day of collection to the project laboratory for immediate processing for flow cytometry and for procurement of viable cells for functional immunology assays.

Project Laboratory Sample Processing & Testing: Upon arrival, mononuclear cell count in whole blood will be determined and, depending on absolute mononuclear cell count, 1 – 2 tubes will be immediately processed for flow cytometry immunophenotyping panels. PBMC will be cryopreserved for innate and adaptive functional studies that will be performed in batch at a later date.

5. LYMPHOMA PATHOLOGY REVIEW

HIV patients show a spectrum of lymphoid hyperplasia that includes some tumor types that are rare in other settings such as plasmablastic lymphoma, primary effusion lymphoma and immunoblastic lymphoma. The AIDS Malignancy Consortium has found that approximately 15% of diagnoses submitted to central review have been substantially changed at review. A tissue block or 10 unstained slides should be sent within 60 days of enrollment to the project laboratory.

6. OPTIONAL RESEARCH SAMPLE FOR UNDEFINED FUTURE RESEARCH

Patients consenting to provide research samples to be submitted to The AIDS and Cancer Specimen Resource Repository for future undefined testing will have an additional baseline peripheral blood sample collected.

Samples Required

A 20 mL peripheral blood sample will be collected in two 10 mL-fill Vacutainer blood tubes (lavender) containing EDTA anticoagulant. Samples will be collected 1-3 weeks prior to initiation of ablative therapy.

Sample Shipment

Transplant centers will ship whole blood tubes by priority overnight FedEx on the day of collection to the ACSR Repository central processing laboratory for sample aliquot processing and sample storage.

Collection and Shipping Procedures and Sample Collection Schedule for Patient Blood Samples for Protocol-Defined Research Testing

RESEARCH TOPIC	RESEARCH SAMPLE	TYPE OF SAMPLE	SAMPLE COLLECTION, PROCESSING AND STORAGE REQUIREMENTS	SAMPLE COLLECTION TIME POINTS	SHIPPING SPECIFICATIONS
Optimizing Diagnostics and Preventative Care for Infections	**Microbial Translocation Markers**	10 mL peripheral blood sample collected in an EDTA containing, lavender-top Vacutainer tube.	Gently mix blood with EDTA by inverting the tube 8-10 times. Store at room temperature while preparing to ship to project laboratory.	**Pre-transplant** Within 1 week of conditioning and day -3 of conditioning **Post-transplant** Days 7, 14 and 100	Peripheral blood tubes will be shipped at ambient temperature on the day of collection, to the Project Laboratory (TBD) by priority overnight FED EX delivery for processing and research testing. Guidelines for specimen handling and shipment to the Project Laboratory is detailed in the BMT CTN 0803 Laboratory Sample Guide.
Characterization of HIV Infection in AIDS-Related Lymphoma	**HIV Load** **Single-Copy PCR** **(Collected only on patients with negative pre-transplant baseline HIV titer by standard assay)**	20 mL peripheral blood sample collected in two 10mL EDTA containing, lavender-top Vacutainer tubes.	Gently mix blood with EDTA by inverting the tube 8-10 times. Centrifuge the EDTA containing whole blood tubes at 1000-1300 x g (~2100 rpm) for 10 minutes within **30 minutes of collection**. Carefully remove the separated plasma (approximately 4-6 mL plasma from each tube, depending on patient hematocrit), and aliquot equally all plasma into three (3) sterile, screw-cap, polypropylene, 5 mL cryovials. Plasma in cryovials will need to be promptly snap frozen and stored at ≤ -70°C in a scientific grade freezer until shipped to the protocol-specified testing laboratory.	**Pre-transplant** Within 1-3 weeks prior to initiation of ablative therapy Within 1 week prior to initiation of ablative therapy **Post-transplant** Days 180, 365 and 730	Plasma aliquots for patients with undetectable baseline HIV viral titers will be shipped frozen twice a year to the Project Laboratory (TBD) by priority overnight FED EX delivery for research testing. Guidelines for specimen handling and shipment to the Project Laboratory is detailed in the BMT CTN 0803 Laboratory Sample Guide.
Plasma DNA Tumor Monitoring	**Tumor Viral DNA Assays, Clonal B-cell DNA**	10 mL peripheral blood sample collected in an EDTA containing, lavender-top Vacutainer tube.	Gently mix blood with EDTA by inverting the tube 8-10 times. Store at room temperature while preparing to ship to project laboratory.	**Pre-transplant** Within 1 week prior to initiation of ablative therapy, and Day -3 of conditioning. **Post-transplant** Days 100, 180, 365	Peripheral blood tubes will be shipped at ambient temperature on the day of collection, to the Project Laboratory (TBD) by priority overnight FED EX delivery for processing and research testing. Guidelines for specimen handling and shipment to the Project Laboratory is detailed in the BMT CTN 0803 Laboratory Sample Guide.

RESEARCH TOPIC	RESEARCH SAMPLE	TYPE OF SAMPLE	SAMPLE COLLECTION, PROCESSING AND STORAGE REQUIREMENTS	SAMPLE COLLECTION TIME POINTS	SHIPPING SPECIFICATIONS
Immune Reconstitution Studies	**T/NK Immunophenotyping, Innate Immune Function, Adaptive Immune Function, Humoral Immune Function**	37 mL peripheral blood sample will be collected in four 8.5 mL-fill ACD solution (yellow top) containing Vacutainer tubes **and** one 3 mL Vacuatiner tube (lavender) containing EDTA...	Gently mix blood the blood tubes with the anticoagulant by inverting the tube 8-10 times. Store at room temperature while preparing to ship to project laboratory	**Post-transplant** Days 60, 180 and 365 post transplant	Peripheral blood tubes will be shipped at ambient temperature on the day of collection, to the Project Laboratory (TBD) by priority overnight FED EX delivery for processing and research testing. Guidelines for specimen handling and shipment to the Project Laboratory is detailed in the BMT CTN 0803 Laboratory Sample Guide.
Lymphoma Pathology Consultation	**Review of Diagnostic Lymphoma Pathology**	A tissue block preferred; 10 unstained slides as an alternative	Store at room temperature while preparing to ship to project laboratory.	Sample should be collected pre-enrolment during the evaluation period and saved. Specimens on enrolled patients will be submitted to project lab within 4 weeks of transplant.	Tissue samples will be shipped at ambient temperature to the Project Laboratory (TBD) by priority overnight FED EX delivery for processing and pathology consultation. Guidelines for specimen handling and shipment to the Project Laboratory is detailed in the BMT CTN 0803 Laboratory Sample Guide.
Optional Investigational Future Research Sample	**Undefined Future Research**	20 mL peripheral blood sample collected in 2-10mL EDTA containing, lavender-top Vacutainer tubes	Gently mix blood with EDTA by inverting the tube 8-10 times. Store at room temperature while preparing to ship to project laboratory.	**Pre-transplant** 1-3 weeks prior to ablative therapy	Peripheral blood tubes will be shipped at ambient temperature on the day of collection, to the Aids Cancer Research Specimen Repository by priority overnight FED EX delivery for processing and research testing. Guidelines for specimen handling and shipment to the Project Laboratory is detailed in the BMT CTN 0803 Laboratory Sample Guide.

APPENDIX D

HIV MANAGEMENT

ANTIRETROVIRALS AND BILIRUBIN

The following antiretroviral medications lead to elevated bilirubin in the absence of other evidence of liver dysfunction.

SUGGESTED PROPHYLAXIS

APPENDIX D

SUGGESTED PROPHYLAXIS

Infectious prophylaxis for HIV patients undergoing HCT will include prophylaxis for:

1. Bacteria: In keeping with the BMT CTN MOP and local institutional standards.
2. Pneumocystits Jiroveci Pneumonia: Prophylaxis will be administered until CD4 counts are >200 and for a minimum of 6 months. Several effective regimens are available. Patient tolerance (nausea, allergic reaction, G6PD or other considerations) may contraindicate a particular regimen. Choices in order of preference are 1) TMP/SMX 1 DS daily 2) TMP/SMX 1 SS daily 3) Dapsone 100 mg daily (may be decreased to 50 mg daily if given in combination with pyrimethamine as described below for toxoplasmosis prophylaxis, 4)Atovaquone 1500 mg daily, 5) Aerosolized pentamidine monthly.
3. Toxoplasmosis: Patients on TMP/SMX do not require additional prophylaxis. If toxoplasma IgG is positive and TMP/SMX cannot be used patients should be prophylaxed for at least 3 months after HCT and until CD4>100. This prophylaxis may be either: 1) dapsone 50 mg po daily and pyrimethamine 50 mg/week and leucovorin 25 mg/week or 2) atovaquone 1500 mg daily plus pyrimethamine 25 mg/day plus leucovorin 10 mg/day
4. Fungi: Anti-fungal prophylaxis will be per local institutional practice. It is noted that in histoplasma endemic areas (Midwest and Puerto Rico) antifungal prophylaxis is standard for CD4 <150 and would be appropriate for at least 3 months after HCT and until CD4>150.
5. HSV/VZV: One of the following regimens should be used for 1 year after HCT unless Acyclovir 400 - 800 mg bid, valaciclovir 500 mg bid, or famciclovir 500 mg po bid.
6. M. Avium Complex (MAC): If CD4 less than 50, Azithromycin suggested at 1200 mg q week or 600 mg twice weekly .
7. Heptatitis:
    a. Patients with positive hepatitis B surface antigen should be evaluated for viral DNA replication (viral load) by a quantitative PCR method before enrolling the patient on the study.
    b. Lamuvudine or newer generation of anti-hepatitis B agents, like Tenofovir, should be started in those with detectable Hepatitis B viral load according to institutional preferences. The goal of the treatment should be achieving undetectable (<500 copies/ml) viral load status before stem cell mobilization chemotherapy.
    c. Patients should be maintained on anti-Hepatitis B treatment throughout the transplant and at least 12 months after the transplant.
    d. Patients with hepatitis-C infection may be enrolled on the trial providing the above Hepatic criteria are met. Anti-hepatitis C treatment with ribavirin and interferon alpha is recommended but not required to be eligible for the study.

e. Liver biopsy must be preformed in patients with Hepatitis-B or C infections if the severity assessment of liver disease based on Child-Turcotte-Pugh (CTP) classification indicates all of the following criteria; Serum bilirubin $\geq$2, serum albumin $\leq$3.5, and INR $\geq$ 1.7

f. Patients with no pathologic evidence of irreversible chronic liver disease such as bridging necrosis and/or significant fibrosis can be eligible for the study.

APPENDIX E

REFERENCES

APPENDIX E

REFERENCES

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