
**AIDS MALIGNANCY CONSORTIUM**

# AMC PROTOCOL #083:

## Tissue Acquisition for Analysis of Prognostic Factors, Immunology, and Genetic Progression of HIV-1 Associated Malignancies

## A Trial of the AIDS Malignancy Consortium (AMC)

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| **Sponsored by:** | National Cancer Institute |
| | Office of HIV and AIDS Malignancies |
| **Collaborator:** | Office of Cancer Genomics |
| **NCT Registration Number:** | NCT01567722 |
| **Protocol Chair:** | Lee Ratner, M.D., Ph.D. (IVR-25383) |
| **Protocol Co-chair:** | Richard Ambinder, M.D., Ph.D. (IVR-10686) |
| | Ariela Noy, M.D. (IVR-28244) |
| | Dirk Dittmer, Ph.D. (NPIVR-44410) |

Version 7.0

NCI Version Date: 25NOV2020

## AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol #083: Tissue Acquisition for Analysis of Prognostic Factors, Immunology, and Genetic Progression of HIV-1 Associated Malignancies (Version 7.0; 25NOV2020),** as written according to AMC, NCI, and FDA guidelines. In accordance with NCI policy, I understand that no deviations from the protocol enrollment criteria or waivers for protocol deviations are permitted.

_____ _____

Signature Date (DDMMMYYYY)

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**Protocol Chair:**
Lee Ratner, M.D., Ph.D.
Washington University School of Medicine
Division of Oncology
660 S. Euclid Ave., Campus Box 8069
St. Louis, MO 63110
Tel: 314-362-8836
Fax: 314-747-2120
Email: lratner@dom.wustl.edu

**Protocol Co-Chairs:**
Richard F. Ambinder M.D., Ph.D.
Johns Hopkins School of Medicine
1650 Orleans Street
CRB1, Room 389
Baltimore, MD 21287
Tel: 410-955-8839
Fax 410-955-0960
Email: ambinri@jhmi.edu

Dirk Dittmer, Ph.D.
Vironomics Core
450 West Dr. Rm 12-056
CB#7295
Chapel Hill, NC 27599
Tel: 919-260-1695
Fax: 919-962-8103
Email: ddittmer@med.unc.edu

Ariela Noy, M.D.
Memorial Sloan-Kettering Malignancy Center
Lymphoma Service
1275 York Avenue
New York, NY 10065
Tel: 212-639-7423
Fax: 646-422-2284
Email: noya@mskcc.org

**Collaborator:**
Nicholas Griner, Ph.D.
Scientific Program Manager
Office of Cancer Genomics
National Cancer Institute
Tel: 978-796-5277
Fax: 301-480-4368
Email: nicholas.griner@nih.gov

**Statistician:**
Jeannette Lee, Ph.D.
University of Arkansas for Medical Sciences
College of Public Health, Biostatistics
4301 W Markham St, Slot 781; Room 3212
Little Rock, AR 72205-7199
Tel: (501) 526-6712
Fax: (501) 526-6729
Email: JYLee@uams.edu

**Data Management/Operations:**
AMC Operations and Data Management Center
The Emmes Company, LLC
401 N. Washington Street, Suite 700
Rockville, MD 20850
Tel: 301-251-1161
Fax: 240-238-2842
Email: amcpm@emmes.com

**AMC Biorepository:**
Sylvia Silver, D.A.
George Washington University Medical Center
Ross Hall, Room 118
2300 I Street NW
Washington, DC 20037
Tel: 202-994-2945
Fax: 202-994-5056
Email: ssilver@email.gwu.edu, amc-bio@emmes.com

## PROTOCOL SYNOPSIS

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| **TITLE:** | Tissue Acquisition for Analysis of Prognostic Factors, Immunology, and Genetic Progression of HIV-1 Associated Malignancies (AMC-083) |
| **ACCRUAL TARGET:** | Up to 200 participants will be enrolled (up to 100 participants with each of the malignancies eligible for participation). |
| **PHASE OF STUDY:** | Observational (biospecimen banking and genetic sequencing) |
| **PARTICIPATING SITES:** | This protocol is open to all AMC member institutions in the U.S. and Latin America. |
| **POPULATION:** | HIV-positive persons age 18 and older with a diagnosis of a malignancy limited to the following diagnoses: diffuse large B cell lymphoma (DLBCL) or non-small cell lung malignancy. |
| **REGIMEN:** | Specimen and data collection at the time of diagnosis and prior to treatment initiation, and data collection at 1 and 2 years after diagnosis. Archival specimens from deceased participants or from participants who are unreachable for informed consent are permitted (with institutional review board [IRB] approval for a waiver of informed consent). Required study specimens include a snap frozen tumor tissue biopsy of minimum size 10 x 10 x 2 mm (approximately 100 mg) OR formalin-fixed, paraffin-embedded (FFPE) (approximately 10-20 mg) tumor tissue biopsy that is sufficiently large to enable extraction of nucleic acids needed for the study, AND separate slides of diagnostic biopsies or other representative tissue for central pathology review. A whole blood sample will be collected and processed for PBMC (this requirement is waived for deceased participants and live participants who are unreachable to provide consent or a blood specimen). If the tissue source site cannot release a FFPE block for sequencing purposes, tissue scrolls and molecular QC slides will be required and cut according to Appendix IV. Specimens will be banked at the AMC Biorepository at George Washington University, which will serve as a Tissue Source Site (TSS) for all AMC sites, for future testing at the Genome Science Center of British Columbia (GSC-BC) for the HIV+ Tumor Molecular Characterization Project (HTMCP). |
| **DURATION:** | Initial specimen and data collection will occur at the time of malignancy diagnosis, prior to treatment initiation. Participants will be followed for up to 2 years after diagnosis to report on clinical outcomes. Archival cases qualifying for a waiver of consent may be submitted with the available follow-up data relative to the diagnosis date for the malignancy. |

**PRIMARY OBJECTIVE:** To obtain high quality, clinically annotated tissue from participant with HIV-1 malignancy. This material will be used to study clinical, genetic, and immunologic parameters, which have prognostic significance and/or are involved in the initiation and progression of HIV-1 malignancies **in the context of the HTMCP initiative**. This will include complete genomic sequence determination of HIV-associated diffuse large B cell lymphomas and non-small cell lung cancer.

## PROTOCOL SCHEMA

**Eligible Participants**

Clinical diagnosis of HIV infection and the presence of one of the following two previously untreated malignancies:

- Diffuse Large B Cell Lymphoma (DLBCL) (plasmablastic lymphoma and primary effusion lymphoma cases are permitted)
- Non-Small Cell Lung Malignancy

**Procedures**

***Collection required prior to treatment initiation (or for deceased participants, at the time of case identification):***

- Tumor tissue biopsy for genomic sequencing
  - Snap frozen tissue sample (minimum size of 10 x 10 x 2 mm, approx. 100 mg)

    OR
  - Formalin-fixed, paraffin-embedded (FFPE) tissue block, or tissue scrolls and molecular QC H&E slides if the site cannot release the tissue block (minimum size approximately 10-20 mg. Fixative buffer pH and age of FFPE sample should be noted)

    Note: Tumor cases without a normal tissue sample and sample types not specified above can still be accepted with written permission from the Office of Cancer Genomic (OCG), and will be included as validation samples.
- FFPE diagnostic tissue block or unstained slides from the block for pathology review*
- Blood for normal Peripheral Blood Mononuclear Cells (PBMC), if available**
- Data collection for enrollment and medical history

***1 and 2 years after enrollment:***

- Data collection for clinical outcomes

**Specimen and Data Submission**

- AMC sites enroll potential participants in AdvantageEDC$^{SM}$ following consent or identification of an archival case (if local requirements for a waiver of consent are met).
- AMC sites ship tissue for genomic sequencing, FFPE tissue for pathology review, and PBMC (if available) to the AMC Biorepository. The AMC ODMC, AMC Biorepository, and OCG will work with AMC sites to coordinate the creation of slides (for QC prior to extraction) and adjacent tissue scrolls for nucleic acid extraction for cases that have passed central pathology if the site cannot release the tissue block for processing by the HTMCP. The AMC Biorepository will transfer the materials to the AIDS and Cancer Specimen Resource (ACSR) for distribution to the HIV Tumor Malignancy Characterization Project (HTMCP).
- The ACSR will:

- Cut unstained slides from the FFPE tissue block for Central Pathology purposes (4 slides for lung tissue or 12 slides for DLBCL), and submit slides to the appropriate Pathology Review Committee for the malignancy type per HTMCP SOPs. Tissue blocks will be returned to sites.
- Batch and ship blood and frozen tissue samples to the GSC-BC.
- If an FFPE tissue block is submitted for sequencing instead of frozen tumor tissue, slides will be cut for molecular QC as well as tissue scrolls per Appendix IV.

- AMC sites enroll cases that pass central pathology review in AdvantageEDC$^{SM}$. Archival cases may be submitted with available follow-up data (1 and 2 years post diagnosis) relating to clinical outcomes within 4 weeks after case acceptance.
- AMC sites will submit required data elements in the HTMCP clinical report forms via upload to the AdvantageEDC Internet Data Entry System within 4 weeks of data collection time points at study entry and 1 and 2 years after diagnosis.

* If the diagnostic tissue block is not available, another representative FFPE tissue block that was collected from an area near the location of the diagnostic biopsy may be submitted for pathology review. The AMC Biorepository will return all tissue blocks to the site after cutting slides for pathology review. The site may submit formalin-fixed, unstained slides for all malignancy types only if the institution will not release a tissue block (4 for lung tissue or 12 for DLBCL tissue).

** Blood samples from live participants may be collected after treatment initiation if necessary. This requirement is waived for deceased participants or from participants with archival tissue who are unreachable for informed consent and a fresh blood sample collection.

# 1.0 BACKGROUND

## 1.1 HIV-Associated Malignancies

HIV infection is associated with a variety of malignancies, including "AIDS-defining cancers" and "non-AIDS-defining cancers" [1]. The AIDS-defining cancers include non-Hodgkin's lymphoma, Kaposi's sarcoma, and cervical cancer. AIDS-defining non-Hodgkin's lymphomas are predominantly diffuse B-cell lymphomas, Burkitt's lymphomas, and less commonly, primary effusion lymphomas and plasmablastic lymphomas. Non-AIDS defining cancers that are increased in prevalence among HIV-1 infected individuals include anal carcinomas, Hodgkin's lymphomas, non-small cell lung cancers, and hepatocellular carcinomas.

There are multiple mechanisms to account for the increased prevalence of malignancies in HIV-1 infected individuals, but these processes have been incompletely characterized in molecular detail. Many HIV-associated malignancies are associated with other oncogenic virus infections. These include members of the human papillomavirus and gamma herpesvirus families, including Epstein-Barr virus and Kaposi's sarcoma herpes virus (KSHV). These infections may be pathogenic in immunosuppressed individuals as a result of an impaired cell-mediated immune response, resulting in chronic and incompletely suppressed infection. Malignancies may also arise from cytokine release from activated T cells induced by HIV infection or other opportunistic infectious agents complicating HIV infection.

Viruses are associated with a variety of malignancy and pre-malignant conditions [2]. Human papillomaviruses are the cause of almost all anogenital carcinomas and approximately 50% of oral malignancies [3, 4]. Epstein-Barr virus is associated with Burkitt's lymphoma, nasopharyngeal and gastric carcinomas, NK/T cell lymphomas, AIDS lymphomas, Hodgkin's lymphomas, post-transplant lymphoma, and pediatric AIDS-associated leiomyosarcomas [5]. KSHV (human herpes virus 8, HHV8) is associated with Kaposi's sarcoma, primary effusion lymphomas, and multicentric Castleman's disease [6]. Human T-cell leukemia virus (HTLV) type 1 causes adult T-cell leukemia and HTLV-associated myelopathy, as well as pneumopathy, uveitis, and immunosuppressive conditions [7]. A recently discovered polyoma virus, Merkel's carcinoma virus, is associated with the majority of cases of Merkel's neuroendocrine skin malignancies. Hepatitis viruses type B (HBV) and C (HCV) are associated with hepatocellular carcinoma, and HCV is also associated with splenic marginal zone lymphomas. Another recently identified virus, xenotropic murine leukemia-related virus (XMRV) may be associated with human prostate malignancy and chronic fatigue syndrome, although this remains controversial [8]. Other viruses have been implicated in collagen vascular, hepatobiliary, and other malignancies, but definitive information is currently lacking [9, 10].

HIV-1 and -2 are associated with immunodeficiency, which predisposes individuals to infections by opportunistic infectious agents, including oncogenic viruses. HIV-associated immunodeficiency also inhibits anti-tumor mechanisms that result in an increased frequency of a variety of tumors [11, 12]. Thus, HIV-1 infection is associated with markedly increased prevalence in AIDS-defining malignancies, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical malignancies, and increased prevalence of non-

AIDS defining malignancies, including: Hodgkin's lymphoma, anal carcinomas, plasma cell neoplasms, and hepatocellular, lung, and testicular malignancies. The effects of HIV and other viruses on mechanisms of tumorigenesis remain to be defined, and this information may provide a solid foundation for new therapeutic approaches.

Comprehensive sequencing of genomes and transcriptomes in cancers that arise in HIV-infected individuals through the HIV+ Tumor Molecular Characterization Project (HTMCP, http://cgap.nci.nih.gov/Cancer_Types) may provide a starting point for a systems biology approach towards understanding differences in pathway activation among identical histological subtypes of cancers in immunocompetent and immunodeficient patients. The results obtained should provide important clues to the pathways that either allow tumors to counteract immune surveillance mechanisms or are redundant in the presence of an extrinsic oncogenic influence such as oncogenic viruses.

## 1.2 Rationale

Rapidly evolving sequencing and informatics tools are substantially diminishing costs of comprehensive characterization of tumor transcriptomes and tumor genomes. These advances have resulted in detailed information on the repertoire of alterations in cancers. Novel approaches of genomic sequencing analyses have provided new tools of pathogens discovery and new information on cellular genetic alterations associated with viral pathogenesis.

The availability of high quality, clinically annotated participant samples is crucial for the study of biologic factors, which influence the progression and treatment response of HIV-1 malignancies. Comprehensive genomic sequences of HIV-associated cancers may identify diagnostic or prognostic disease signatures, and recurrent "driver" alterations that may be targets for new therapies. It is also possible that the comparison of transcriptomes and genomes between lymphomas from $HIV^+$ and $HIV^-$ individuals might identify novel non-human sequences that could potentially suggest the presence of transcripts from hitherto undiscovered oncogenic viral agents.

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer related alterations in HIV+ participants and HIV- participants. It is possible that the comparison of transcriptomes and genomes between tumors from HIV+ and HIV- individuals may or may not identify novel non-human sequences, which could suggest the presence of transcripts from known or hitherto undiscovered oncogenic viral agents. This protocol serves to collect specimens for banking at the AMC Biorepository, for future testing at the Genome Science Center of British Columbia (GSC-BC) for the HIV+ Tumor Molecular Characterization Project (HTMCP).

The current study will investigate genomic sequences in two different HIV-1-associated malignancies: diffuse large B cell lymphoma and lung cancer. Lymphoma was chosen as an AIDS-defining malignancy that occurs more frequently in HIV-positive individuals compared to HIV-negative individuals [13,14]. However, only diffuse large B cell lymphoma (including plasmablastic lymphoma [PBL] and primary effusion lymphoma [PEL]) will be included in this study, as Burkitt lymphoma is studied independently in

another protocol, and occurs with a lower frequency. Two other malignancy types, anal cancer and cervical cancer, were initially included in this protocol: enrollment of anal cancer cases was discontinued with protocol version 4.0 due to the rarity of identifying tumor tissue samples of sufficient size for this protocol's tissue requirements, and enrollment of cervical cancer cases was discontinued with protocol version 6.0 due to overall HTMCP accrual completion for these cases. Lung cancer and diffuse large B cell lymphoma were chosen for comparison to full genomic sequence data that has been obtained for the corresponding malignancies in HIV-negative individuals to determine if there are differences in the pathogenesis of these disorders in the HIV-1-positive versus HIV-1-negative participants [15, 16, 17].

## 2.0 OBJECTIVE

The primary objective of this project is to obtain high quality, clinically annotated tissue from participants with HIV-1 malignancy. This material will be used to study clinical, genetic, and immunologic parameters, which have prognostic significance and/or are involved in the initiation and progression of HIV-1 malignancies in the context of the HTMCP initiative. This will include complete genomic sequence determination of HIV-associated diffuse large B cell lymphomas and lung cancer.

## 3.0 ELIGIBILITY CRITERIA

A rostered AMC investigator must document that each protocol participant meets all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

**NOTE**: Institutions may use this section of the protocol as an eligibility checklist for source documentation if it has been reviewed, signed, and dated before registration/randomization by the study investigator. If used as source documentation, this checklist must be printed, the investigator must check each item to document their assessment that the participant meets each eligibility criterion, and the completed checklist must be maintained in the participant's chart.

Participant ID Number: 083 - ___ ___ ___ - ___ ___ ___

Patient's Initials (L, F, M (optional)): ___ ___ ___

**NOTE**: All questions regarding eligibility should be directed to the study chair.

### 3.1 Inclusion Criteria

3.1.1 Malignancy diagnosis. Participants must have a diagnosis of HIV-associated malignancy of one of two types:

- All variants of Diffuse Large B Cell Lymphoma (except Burkitt's lymphoma).
- Non-Small Cell Lung Malignancy

3.1.2 Previous chemotherapy: tumors will be accepted that have had previous neoadjuvant/chemotherapy treatment, but the specific treatment regimen must be noted and communicated to the OCG.

3.1.3 Previous malignancies: tumors from participants with previous malignancies will be accepted, but any previous malignancies must be noted and communicated to the OCG.

3.1.4 HIV diagnosis. HIV infection based on serologic documentation of HIV infection at any time prior to study entry, as evidenced by positive ELISA, positive Western Blot, or any other FDA-approved (licensed) HIV test. Alternatively, this documentation may include a record that another physician has documented that the participant has HIV based on prior ELISA and western blot, or other approved diagnostic tests.

3.1.5 Age. Participants must be ≥ 18 years old, in order to focus on adult oncology participants and in light of differences in tumor mutational spectrum that are likely to be found in pediatric compared to adult tumors.

3.1.6 Informed Consent. Unless the IRB of record has granted a waiver of the requirement to obtain informed consent from participants with archival specimens who cannot be contacted or the participant is deceased, participants must be willing and able to sign an IRB-approved informed consent document that permits the use of samples for genomic-based molecular characterization projects.

3.1.7 Complete Case Requirements. The site must ensure the minimum specimen requirements for HTMCP case submission can be met, including the availability of/ability to collect:

- Tumor tissue for genomic analysis that was collected prior to initiating treatment for the malignancy (preferable). Repeat tumor biopsy will not be performed solely to meet the protocol specimen collection requirements. Acceptable tissue includes:
  - Flash-frozen diagnostic tumor biopsy tissue (minimum specimen size of 10 x 10 x 2 mm, approximately 100 mg).
  - FFPE tumor biopsy material tissue, which may include a tissue block OR tissue scrolls and slides for molecular QC (see Appendix IV) if a block is not released.
  - Tumor tissue sample with specifications other than those noted above for which the Office of Cancer Genomics (OCG) has provided written approval for submission to project.Tumor cases without a normal tissue sample can still be accepted with written permission from OCG, and will be included as validation samples.
- A 10 ml blood specimen for PBMC isolation. For live participants, blood samples should be collected prior to treatment initiation for the malignancy if possible, but may be collected after treatment initiation if necessary. This requirement is waived for deceased participants or live participants who are unavailable to provide a whole blood sample.
- Diagnostic FFPE tissue block for central pathology review. If the diagnostic tissue block is not available, another representative FFPE tissue block that was collected from an area near the location of the diagnostic biopsy may be submitted for pathology review. The site may submit formalin-fixed, unstained slides for all malignancy types only if the institution will not release a tissue block (4 slides for lung tissue or 12 slides for DLBCL tissue).
- Completed HTMCP enrollment form for the applicable tumor type.

## 3.2 Exclusion Criteria

Participants who do not fulfill the criteria as listed in Section 3.1 above, are ineligible. Additionally**,** the presence of any of the following conditions will exclude a participant from study enrollment:

### 3.2.1 Participant can be contacted but is unwilling or unable to provide informed consent.3.3 Accrual Targets

3.3.1 Number of participants to be enrolled: Up to 200 participants will be enrolled, including up to 100 participants with each of the 2 eligible malignancies.

3.3.2 Accrual rate: The anticipated accrual period is 8 years or more (accrual rate of 6 participants per month).

## 4.0 DATA ENTRY

### 4.1 Participant Enrollment Procedures

4.1.1 Institutional requirements for enrollment: Sites must have this protocol approved by their Institutional Review Boards (IRB) and be registered for study participation with the AMC Operations and Data Management Center (ODMC) before they may enroll participants. Additionally, participating institutions must submit a completed Institutional Certification for the submission of study data to the NIH Database of Genotypes and Phenotypes (dbGaP) before transmitting samples or data for this project. A template institutional certification letter is provided among the protocol-specific materials for this project at www.AIDSCancer.org and in OCG Template #105, Institutional Certification for Participation in Office of Cancer Genomics Policy, available online at: https://ocg.cancer.gov/sites/default/files/HTMCP_SOP_manual.pdf.

4.1.2 Screening enrollment and sample collection

After obtaining informed consent from a potential participant (or for deceased or archival cases from unreachable participants, identifying an eligible case), the site will collect tumor tissue and records to confirm the participant's diagnosis and determine eligibility. AMC sites will initiate case submission by registering the participant via the AMC AdvantageEDC Internet Data Entry System. The participating site will ensure the participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist in AdvantageEDC (Segment A registration).

Both GlobalTrace[SM] and HTMCP specimen ID labels will be used for tracking specimens prior to acceptance by the HTMCP. All sites will be provided GlobalTrace labels for use in submitting specimens for eligibility review. The AMC Biorepository will be provided pre-printed HTMCP specimen ID labels to affix to submitted specimens before shipping to the appropriate laboratory. Only HTMCP specimen IDs will be tracked by OCG once the case is accepted for genomic sequencing.

Participating sites will collect data in the applicable enrollment form for the malignancy type in the HTMCP's paper forms, which are available among the protocol-specific materials for this project at www.AIDSCancer.org and will be attached to the enrollment notification for Segment A. The HTMCP Enrollment Form must be completed and uploaded in AdvantageEDC following Segment A registration for eligibility review by the project. Original copies of the HTMCP enrollment form must be maintained at the site.

4.1.3 Specimen submission and eligibility review

All required specimens must be submitted to the AMC Biorepository following registration in AdvantageEDC. Failure to submit any required specimens will result in case rejection.

Once received at the AMC Biorepository, the AMC Biorepository will confirm that

all required specimens (e.g., tumor tissue for genomic sequencing, tumor tissue for pathology review, and/or PBMC) have been received, will prepare tissue sections or scrolls as necessary, prepare slides for central pathology review as required, and will distribute specimens for central pathology/case eligibility review. The AMC ODMC will provide enrollment information to OCG to review cases for inclusion in the project. OCG will communicate case acceptance to OCG's designee (Nationwide Children's Hospital [NCH]) and the AMC ODMC.

#### 4.1.4 HTMCP enrollment

Following notification of case acceptance from OCG, the AMC ODMC will enroll the participant in Segment B of protocol AMC-083 in AdvantageEDC. The AMC ODMC will also enroll the participant in the HTMCP's data entry system, maintained by NCH, using data provided in the Enrollment Form.

## 4.2 On-Study Data Entry Procedures

Participating sites will collect data for the one and two years post diagnosis follow up time point in the Follow-up form for the applicable malignancy type in the HTMCP's paper forms, which are available among the protocol-specific materials for this project at www.AIDSCancer.org. Completed HTMCP follow-up forms must be uploaded in the appropriate area of AdvantageEDC within 4 weeks before or after the target form submission deadline. For participants providing archived tissue specimens for genomic analysis, the Follow-up Form for the applicable malignancy type and duration since initial diagnosis will be due within 4 weeks of case acceptance. Original copies of the HTMCP Follow-up Forms must be maintained at the site.

## 5.0 SAMPLE ACQUISITION AND PROCESSING

### 5.1 Sample Acquisition

Samples will be obtained and processed using protocols developed for the HTMCP. These protocols can be found online at http://ocg.cancer.gov/resources/ocg-templates-and-protocols. All samples will be obtained for the purposes of this study after the participant has provided informed consent. If the participant consents to provide previously collected tissue samples available from pathology for the baseline samples, a piece of the pathology specimen or the tissue block will be obtained for research purposes. Participants will not be re-biopsied solely for the purpose of sample collection. Retrospective cases may be submitted with the available follow-up data relative to the diagnosis date, if available.

#### 5.1.1 Tumor tissue biopsy

All eligible participants will have biopsy tissue banked as part of this study. When clinically indicated, these participants will undergo biopsy of a lymph node or other organ involved with malignancy or a suspected malignancy. Biopsies must be surgical biopsies done in the operating room. After the necessary samples are obtained for the optimal medical care of the participant, a second tissue biopsy will be collected for the purposes of this protocol and submitted to the AMC Biorepository. The additional pieces of tissue must measure about 10 x 10 x 2 mm (approximately 100 mg per piece) (minimal amount of tissue required) and will be snap frozen within 20 minutes of the time tissue is removed from the participant. Do not freeze tissue pieces larger than this size or mass. The method of snap freezing and transport of frozen tissues is described in Appendix IV. The time between specimen collection and freezing must be recorded.

If fresh frozen tissue is unavailable, a FFPE (approximately 10-20 mg) tissue block may be submitted for genomic sequencing OR tissue scrolls if the site will not release the tissue block. Archival samples are permitted. Fixative buffer pH should be noted. If the FFPE tissue block is submitted for genomic analysis, the tissue block should be submitted to the AMC Biorepository for preparation of the tissue scrolls and molecular QC slides. The tissue block will be returned to the site after preparation of the slides. If the site will not release the tissue block to the AMC Biorepository after the case has passed central pathology review the AMC ODMC and OCG will work with the AMC site to adhere to the tissue scroll procedures described in Appendix IV. The site will be required to produce the necessary molecular QC H&E slides and tissue scrolls to be shipped to GSC-BC within 24 hours of cutting scrolls. Alternatively, tumor tissue samples not meeting the specifications noted above may be submitted to the project ONLY with prior written approval from the Office of Cancer Genomics. Documentation of this approval must be provided to the AMC ODMC at the time of enrollment in AdvantageEDC.

AMC sites will send additional tissue to the AMC Biorepository for pathology review (Appendix IV). If the diagnostic tissue block is not available, another representative FFPE tissue block that was collected from an area near the location of the diagnostic biopsy may be submitted for pathology review. The site may

submit formalin-fixed, unstained slides for all malignancy types only if the institution will not release a tissue block (4 slides for lung tissue or 12 slides for DLBCL tissue). **A FFPE block is preferred**.

FFPE tissue collected for genomic analysis may not be submitted for the tissue requirements for pathology review. Separate tissue slides must be submitted to or prepared by the AMC Biorepository for pathology review. The AMC Biorepository will cut slides from the FFPE block and distribute all slides for pathology review according to HTMCP SOPs. The AMC Biorepository will return all tissue blocks to the site after cutting slides for pathology review. Frozen tumor tissue or FFPE tissue scrolls will be sent to GSC-BC for genomic analysis.

5.1.2 Peripheral blood mononuclear cells (PBMC) sample for germline DNA

All live participants in this study who are able and willing to provide a blood sample will have one 10 mL sample of peripheral blood drawn by venipuncture or cannulation of an indwelling venous access device. This sample will be used for germline DNA analysis. This blood draw will occur at the same time as a blood draw for routine medical care. Sites submitting tumor samples collected retrospectively may still collect a blood sample for PBMC even if the participant has already started treatment for the malignancy.

Samples will be collected in a tube containing either EDTA or acid citrate dextrose (ACD) anticoagulant and transported to the local laboratory for processing PBMC within 2 hours of collection (according to HTMCP SOP#206, Processing Non-Tumor Samples for the HIV+ Tumor Molecular Characterization Project, Blood Cells). PBMC samples should be prepared and frozen according to Appendix III to prevent hemolysis. After processing blood samples for PBMC, the site will ship frozen samples to the AMC Biorepository in accordance with Appendix IV. Please contact the AMC ODMC with questions about processing blood for PBMCs; alternate processes for PBMC isolation may be approved at the discretion of OCG.

If the initial PBMC sample submitted is found to be insufficient for normal DNA analysis, OCG and/or the AMC ODMC will notify the site that an additional blood specimen may be collected from the participant. The additional blood specimen must be processed for PBMC in accordance with the requirements listed above.

## 5.2 Sample Storage

5.2.1 Sample identification and assurance of anonymity

Participant material will be obtained in the inpatient or outpatient setting. In either case, samples of tumor, blood, bone marrow, and/or skin will be initially identified with a 9-digit AMC participant ID number in the AdvantageEDC and GlobalTrace systems. All study specimens will be shipped to the AMC Biorepository.

5.2.2 Deposition of samples in the laboratory

The principal investigator or his/her designee will be responsible for shipping specimens to the AMC Biorepository in accordance with Appendix IV. Specimens shipped to the AMC Biorepository will be identified by participant ID and sample

number. The AMC Biorepository will transfer specimens to the ACSR for storage. Samples will be stored at the ACSR at -80°C or colder. The ACSR will be responsible for following the HTMCP SOPs as they relate to sample handling, labeling, and shipping.

## 5.3 Biopsies Negative for Malignancy

If biopsy is performed for the purpose of diagnosing suspected malignancy, and the biopsy submitted for the purposes of this protocol is later found to be negative for malignancy, no additional tissue specimens will be collected for the purpose of this study and no health information will be recorded in the study database. Unless the participant provides consent for ACSR donation for the future use of his/her specimens, all study samples collected from participants who are found negative for malignancies will be destroyed.

## 5.4 Sample Analysis

Frozen and FFPE samples will be stored at the ACSR until shipping is arranged to the GSC-BC. At the GSC-BC, samples will undergo genomic analysis using study-generated ID numbers. PHI will never be available to investigators involved with any stage of the genomic analysis.

Samples will be analyzed at the GSC-BC by full genomic sequence analysis. For this purpose, DNA will be extracted, sheared, and Illumina sequencing performed in order to obtain 80x genome coverage. Comparisons will be made between tumor and normal DNA to identify the somatic changes associated with cancer. Frequency of mutations within a sample will be determined by deep sequence analysis. RNA will be sheared, reverse transcribed, and sequenced to assess transcribed sequences.

Genomic analyses performed on these samples may include, but are not limited to, array-based gene expression profiling, comparative genome hybridization, and single nucleotide polymorphism studies, as well as whole genome sequencing analysis using the most current genomic technology available. The goal of comprehensive genomic analysis is to document all the genetic abnormalities associated with malignancy and other virus malignancies.

To facilitate discovery and collaboration, de-identified DNA sequences from consenting participants will be shared with other investigators performing similar research. De-identified retrospective cases may be submitted with the available follow-up data relative to the diagnosis date.The way in which this genetic information is shared is described in Appendix II. As the AMC is a Federally-funded cooperative group, the AMC is obligated to disseminate research findings. This will be facilitated by sharing genetic testing results from all AMC specimens collected on this protocol using registries such as dbGaP, the Database of Genotypes and Phenotypes. Data submitted to dbGaP includes sensitive information; however, this information, such as de-identified phenotypes and genotypes for individual study participants, will only be available via a controlled-access database. All data entry in dbGaP for this study will be performed by GSC.

Controlled-access data can only be obtained if a user has been authorized by the appropriate Data Access Committee. All AMC members have access to information obtained from AMC samples.

dbGaP also provides an open level of access, but this involves only the release of non-sensitive data such as the study summary and/or protocol document, the contents of measured variables in aggregate, and genotype-phenotype analyses. Submitters to dbGaP must identify any limits on the use of data specifically set through the informed consent form (either as a whole or on a case-by-case basis) and their IRB must review and provide GWAS institutional certification for the submission of data (template Institutional Certification available at HTMCP SOP#105).

## 6.0 CLINICAL INFORMATION AND MAINTENANCE OF AN HIV-MALIGNANCY DATABASE

### 6.1 Data Collection

Details of clinical information are in the protocols for each malignancy type in the HTMCP SOP manual.

For participants of interest (i.e., participants whose samples will be sequenced), complete clinical information will be obtained. Information will be obtained by the investigators through review of the participant's inpatient and outpatient medical records and by discussing the case with the participant's physicians. Information will include demographics (race, ethnicity), vital status of the participant, date of last contact with the participant, history of the presenting illness, history or prior malignancy, date of pathological diagnosis, method of initial pathologic diagnosis, neo-adjuvant therapy and other therapies prior to tissue procurement and response to each therapy, date of tissue collection and fixative buffer pH (if applicable), date or progressive disease if applicable, primary site of progressive disease if applicable, surgical resection date if applicable, tobacco use history, date of HIV diagnosis, prior AIDS defining co-morbidities, co-infections, HAART treatment prior to and at time of malignancy diagnosis, HIV risk group, history of other malignancies, cause of death and duration from diagnosis to death if applicable, relevant past medical history, Karnofsky or ECOG performance score, information regarding the physical exam, results of initial laboratory tests (hemoglobin, LDH, uric acid including CD4 count at nadir and time of malignancy diagnosis, HIV RNA load at time of malignancy diagnosis) and imaging tests, results of the diagnostic tumor biopsy and bone marrow biopsy, and results of flow cytometry, cytogenetics, and molecular studies.

### 6.2 Duration of Follow-up Data Collection

Participants will be followed prospectively to record the types of treatment given, and treatment outcome and toxicity. Follow-up information will include the results of subsequent laboratory and imaging tests, pathology, cytogenetic and molecular diagnostic reports, and records describing the participant's course in the inpatient and outpatient setting.

Participants will remain on study for data reporting purposes for up to 2 years after enrollment. Data abstraction for follow-up will occur at 12 and 24 months (± 4 weeks) after the date of initial diagnosis stated in the HTMCP enrollment form. Follow-up forms will be completed using the HTMCP's paper forms and will be submitted via forms upload in AdvantageEDC. The Follow-up Form will be requested for the 1 and 2 year milestones for accepted cases. In the event the participant declines further participation, expires, is lost to follow-up, or is removed from study follow-up by the investigator, the Off Study Form must be submitted in AdvantageEDC.

## 6.3 Recording Information in the Database

Information will be entered into the HTMCP forms and reviewed by the principal investigator at each site or his/her designee. Only the PI and those who enter the data will have access to the database at the AMC sites. Data forms will be uploaded into AdvantageEDC. The AMC ODMC will enter all data from submitted forms in the HTMCP's database.

## 7.0 DISTRIBUTION OF SAMPLES TO RESEARCHERS

All material(s) received by the AMC Biorepository at George Washington University (GWU) will be transferred to the AIDS and Cancer Specimen Resource (ACSR) within 24 hours of receipt.

The specimens collected under this protocol are primarily for the use of the Genome Science Center (GSC) in fulfillment of their role as characterization center for the HIV Tumor Molecular Characterization Project. All collected samples will be sent to GSC-BC for validation and characterization. Returned remnant specimens and associated clinical information can be requested by AMC investigators, the NCIs Genome Science Center and other investigators through a Letter of Intent (LOI) to the ACSR. Requests should include rationale for the study, proposed analysis, type and quantity of specimens, and clinical information required. Approval from the Human Research Protection Office of the requestor's institution will be required for studies using samples from the tissue repository.

The ACSR's independent review panel will evaluate LOIs based on factors including, but not limited to, scientific merit, availability of samples, and scientific priorities. Once an LOI is approved, the ACSR will send the specimen to the approved party and will work with the AMC ODMC and GSC to obtain the requested clinical information in a coded and de-identified fashion.

The ACSR will serve as the "honest broker" and will be responsible for linking the data and specimens by UPN prior to providing information to researchers who wish to obtain linked data and specimens to minimize the risk of breach of confidentiality.

Individual results/data from any study using material from the tissue repository will not be disclosed to the participant or physician except in extraordinary circumstances when nondisclosure is deemed to be unethical and then only after consultation with the Human Research Protection Office of each university.

## 8.0 POTENTIAL RISKS

As a laboratory study involving only sample collection through routine clinical care and data abstraction, no adverse events will be collected for this study.

### 8.1 Risks of Tumor or Node Biopsy

For some participants, the tumor specimen will be acquired via a lymph node biopsy or a biopsy of an extranodal site, including bone marrow. The risks of the biopsy vary with the site, but generally include local discomfort, bleeding, and infection. All participants on study will have the biopsy performed in the course of routine medical care.

Participation in the study will entail no additional risks attributable to the procedure if the malignancy specimen is obtained via a surgical biopsy for routine medical care.

### 8.2 Risks of Blood Collection

There is a very small risk of infection or bleeding associated with venipuncture.

### 8.3 Breach of Confidentiality

Despite the extensive security measures employed to de-link the identities of participants and their donated tissue specimens, there is a possibility that the identities of participants enrolled in this study could be discovered or linked to genetic sequence data obtained from their tissue specimens. Consequently, it is possible to use this information to link them to the identities of their children, parents, siblings, and other relatives. It may be possible to identify participants as carriers of genetic mutations. It is also possible that there could be violations of the security used to store the codes linking participant's genetic information.

## 9.0 STATISTICAL CONSIDERATIONS

This is a descriptive study of the mutational spectrum in each type of HIV-1 associated malignancy. No statistical analyses are planned for this protocol.

## 10.0 ROLE OF DATA MANAGEMENT

### 10.1 CRF Instructions

Instructions concerning the recording of study data on the HTMCP's paper CRFs will be provided by the NCH and made available to participating sites by the AMC ODMC at www.AIDSCancer.org. Fillable PDF forms will be used for all clinical data collection for the HTMCP. All forms will be uploaded in AdvantageEDC for tracking purposes. The AMC ODMC will manage all data entry in the HTMCP project database (managed by the NCH) on behalf of sites.

### 10.2 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study (See Appendix I, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study database.

### 10.3 Data Monitoring

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

## 11.0 ETHICAL CONSIDERATIONS

### 11.1 Informed Consent

The principles of informed consent described in Food and Drug Administration (FDA) regulations (45 CFR Part 46) must be followed. The AMC ODMC must receive a copy of the letter of approval from the IRB, which specifically approves the protocol and informed consent, before participant enrollment. The IRB must also approve any significant changes to the protocol and documentation of this approval must be submitted to the AMC ODMC. Records of all study review and approval documents must be kept on file by the Investigator and are subject to inspection during or after completion of the study. Any AEs related to the study procedures must be reported to the IRB in compliance with local requirements. The IRB should receive notification of completion of the study and final report within 3 months of study completion and termination. The Investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

All living participants who are reachable to approach for participation will be required to provide written informed consent prior to inclusion of their samples in the tumor bank. Unless a waiver is granted for the requirement for the informed consent process for participants who cannot be contacted, the consent must be freely given, with the understanding that it may be withdrawn at any time, and the informed consent form must be given in writing.

If for any reason a participant in the study withdraws consent for the continued research use of the tissue samples, the samples will be disposed according to Institutional or ACSR guidelines on the handling of medical waste, depending on the party that has possession of the samples at the time of withdrawal.

#### 11.1.1 Request for a waiver of the requirement for informed consent

A request to waive the requirement to obtain informed consent is being requested with protocol version 7.0 for archival sample and data collection and analysis for participants who cannot be reached for a consent discussion.. A model informed consent document is available if the IRB at a participating site denies a waiver of consent. Deceased participants may be included provided that the data are recorded as described below; research involving deceased persons is not considered human subjects research.

The investigator believes this study meets the following requirements for this request per 46 CFR 46.116(d). The pre-2018 Human Subjects Protections regulations are cited as follows, as the trial ws initiated at participating centers under these regulatory requirements:

- The research involves no more than minimal risk to the participants. The only risk is the loss of patient confidentiality, which will be minimized as described in the confidentiality section (Section 8.3).
- The waiver or alteration will not adversely affect the rights and welfare of the participants. There will be no contact with the participants or their next of kin

and no documentation of this study in their medical records.

- The research could not practicably be carried out without the waiver or alteration. As described above, these diseases are very rare, and consent of live participants for archival cases is not feasible for all available cases. Consent of deceased participants is not feasible. Enrollment of the trial in a reasonable time frame has not proven feasible without access to archival specimens .
- The project could not practicably be conducted without the use of PHI. PHI collected will be limited to dates, such as the year of diagnosis, treatment, response, and diagnosis. Collection of select dates is necessary to obtain data elements that are required to determine participant eligibility and are important to the question being studied. The AMC also requires collection of demographic data (participant initials, birth date, and zip code) in standard forms for audit verification, assurance that each participant enrolled is unique, and required demographic reporting to the NCI. These details will be removed from the dataset before transfer to OCG, with birthdate converted to age.
- An adequate plan to protect identifiers from improper use and disclosure is included in the research proposal. Only authorized study personnel have access to this information in AdvantageEDC, which is secured from unauthorized access with login/password controls. Participant initials are encrypted in the AdvantageEDC data entry system and in the study database, and can only be viewed in AdvantageEDC by the clinical site staff. Access of de-identified records through the HTMCP and dBGaP is described in Section 6.1 and Section 7.0.
- An adequate plan to destroy the identifiers at the earliest opportunity, or justification for retaining identifiers, is included in the research proposal. The PHI collected is a component of standard AMC data entry forms for compliance with NCI demographic reporting requirements, and is also required for data analysis. Protections for this information will be applied as stated above.
- The project plan includes written assurances that PHI will not be reused or disclosed for other purposes. Data access will be restricted to the parties listed in Section 7.0 and will not be reused or disclosed for any other purpose. No PHI, including dates, will be included in any study publications.
- The AMC routinely provides study summaries for participants on its website.

A waiver of HIPAA Authorization is being requested for this study. As described above, the use or disclosure of PHI involves no more than minimal risk; granting of the waiver will not adversely affect privacy rights or the welfare of the individuals whose records will be used; the project could not practicably be conducted without a waiver; and the project could not practicably be conducted without use of PHI. Further, the privacy risks are reasonable relative to the anticipated benefits of research, as the importance of the knowledge that may reasonably be expected to result outweighs the minimal risk posed to participants. PHI will not be re-used or disclosed for other purposes and, whenever appropriate,

the participants will be provided with additional pertinent information after participation. In accordance with Good Clinical Practice and the retention of records under 45 CFR 46.115, study records will not be destroyed until at least three years after the completion of the research. Only de-identified data will be retained.

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local and state laws and regulations governing the confidentiality and disclosure of health information.

## 11.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by the Investigator and the IRB/IEC before implementation.

## 11.3 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Consortium (AMC). As part of their contractual obligations, each participating site within the AMC and the AMC as a whole is required to assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

| **Accrual Targets** | | | | | |
|---|---|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | | | |
| | **Females** | | **Males** | | **Total** |
| Hispanic or Latino | 24 | + | 47 | = | 71 |
| Not Hispanic or Latino | 43 | + | 86 | = | 129 |
| **Ethnic Category: Total of all subjects** | 67 (A1) | + | 133 (B1) | = | 200 (C1) |
| **Racial Category** | | | | | |
| American Indian or Alaskan Native | 1 | + | 3 | = | 4 |
| Asian | 1 | + | 3 | = | 4 |
| Black or African American | 24 | + | 46 | = | 70 |
| Native Hawaiian or other Pacific Islander | 1 | + | 1 | = | 2 |
| White | 40 | + | 80 | = | 120 |
| **Racial Category: Total of all subjects** | 67 (A2) | + | 133 (B2) | = | 200 (C2) |
| | (A1 = A2) | | (B1 = B2) | | (C1 = C2) |

## 11.4 Confidentiality

Breach of confidentiality is likely the greatest risk of participating in this study. Every effort will be exerted to minimize this risk. Maintaining confidentiality of both specimens and clinical data will be the responsibility of the principal investigator and staff (which includes but is not limited to the staff of the laboratory and the study coordinator).

It may be desirable to contact participants at a later time to request additional information or to solicit participation in therapeutic trials. If the participant agrees to future contact as

discussed in their consent, the participant will first be contacted by one of the investigators of this study. If the participant agrees, then contact information will be provided to the Principal Investigator of the other trial. Whether a participant consents to future contact will be tracked in the study database.

## 12.0 REFERENCES


1. Boshoff C, Weiss R: AIDS-related malignancies. *Nature Reviews in Cancer* 2002, 2:373-382.
2. Moore PS, Chang Y: Timeline: Why do viruses cause cancer? Highlights of the first century of human tumour virology. *Nature Reviews in Cancer* 2010, 10:878-888.
3. zurHausen H: Papillomaviruses in the causation of human cancers - a brief historical account. *Virology* 2009, 384:260-265.
4. Marur S, D'Souza G, Westra WH, Forastiere AA: HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncology* 2010, 11:781-789.
5. Pattle SB, Farrell PJ: The role of Epstein-Barr virus in cancer. *Expert Opinions in Biological Therapy* 2006, 6:1193-1205.
6. Wong EL, Damania B: Linking KSHV to human cancer. *Current Oncology Reports* 2005, 7:349-356.
7. Barmak K, Harhaj E, Grant C, Alefantis T, Wigdahl B: Human T cell leukemia virus type I-induced disease: pathways to cancer and neurodegeneration. *Virology* 2003, 308:1-12.
8. Silverman RH, Nguyen C, Weight CJ, Klein EA: The human retrovirus XMRV in prostate cancer and chronic fatigue syndrome. *Nature Review in Urology* 2010, 7:392-402.
9. Mason AL, Zhang G: Linking human beta retrovirus infection with primary biliary cirrhosis. *Gastroenterology Clinical Biology* 2010, 34:359-366.
10. Perl A, Fernandez D, Telarico T, Phillips PE: Endogenous retroviral pathogenesis in lupus. *Current Opinion in Rheumatology* 2010, 22:483-492.
11. Boschoff C, Weiss R: AIDS-related malignancies. *Nature Reviews in Cancer* 2002, 2:373-382.
12. Silverberg MJ, Abrams DI: AIDS-defining and non-AIDS defining malignancies: cancer occurrence in the antiretroviral therapy era. *Current Opinion in Oncology* 2007, 19:446-451.
13. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008;148:728-736.
14. Chirenje ZM. HIV and cancer of the cervix. Best Pract Res Clin Obstet Gynaecol. 2005;19:269-276.
15. Lee W, Jiang Z, Liu J, et al. The mutation spectrum revealed by paired genome sequences from a lung cancer participant. Nature 2010; 465:473–477.
16. Pasqualucci L, Trifonov V, Fabbri G, Ma J, Rossi D, Chiarenza A, Wells VA, Grunn A, Messina M, Elliot O, Chan J, Bhagat G, Chadburn A, Gaidano G, Mullighan CG, Rabadan R, Dalla-Favera R. Analysis of the coding genome of diffuse large B-cell lymphoma. Nat Genet. 2011 Jul 31;43(9):830-7.
17. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol. 2011 Feb;12(2):175-80.

## APPENDIX I: AMC DATA AND SAFETY MONITORING PLAN

Version 9.0 • October 6, 2020

### Introduction

The AIDS Malignancy Consortium (AMC) Data and Safety Monitoring Plan (DSMP) outlines the measures employed by the group to monitor the safety of participants and ensure the data validity and integrity for all clinical trials it conducts. This includes methods to: 1) monitor the progress of trials and the safety of participants; 2) comply with regulatory requirements for adverse event (AE) reporting; 3) processes for trial termination or temporary suspension and major modifications; and 4) plans for ensuring data accuracy and protocol compliance. As the AMC conducts protocols of varying research phase, region of conduct (which may include trials conducted in the U.S., international sites, or both), IND sponsor (AMC investigator, CTEP, or industry-sponsored) and clinical data entry system use, this plan addresses broad processes applying to the range of trial designs and requirements. Refer to the individual AMC protocol to identify the applicable study characteristics for the relevant requirements described in this plan.

### Monitoring the Progress of Trials and the Safety of Participants

*Routine and expedited AE reporting*

All AMC protocols that collect safety data adhere to the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm), as applicable to the clinical protocol. AEs are to be recorded in the source documents, assessed by a clinical investigator for the AE reporting criteria, and promptly reported in the clinical data entry system as required by each protocol. For AMC trials conducted under a CTEP IND and AMC trials conducted within the U.S., all AEs that meet the NCI's expedited reporting requirements are reported to the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application, either directly or through integration with Medidata Rave where this system is employed for AMC protocols. Use of this system ensures notification to the protocol chair and Investigational Drug Branch (IDB) at CTEP, as required for trials conducted under a CTEP IND, and a uniform expedited reporting and safety review process for AMC domestic trials. The system may also be programmed to include sponsor notification as required for trials with industry support. Alternate process for expedited AE reporting to the AMC protocol chairs and AMC Operations and Data Management Center (ODMC) within the clinical data entry system (AdvantageEDC or Advantage eClinical only) may be defined in the protocol for select trials (international studies and The ANCHOR Study).

All serious adverse events (SAEs) received by the AMC ODMC will be reviewed by the AMC medical monitor at the AMC ODMC for consideration of individual participant safety, safe trial conduct, data reporting quality for AE term selection, and appropriate application of the regulatory criteria for seriousness, expectedness, and relatedness to the investigational therapy. If alternate procedures are followed for SAE review, the process for adequate medical monitoring will be defined in the AMC protocol and the Transfer of Regulatory Obligations (TORO) with the sponsor. AMC medical monitor review includes review of the CTEP-AERS report before CTEP submission for IDB review (if applicable), or review of the SAE report in the data entry system for trials not using CTEP-AERS for expedited reporting. The IND sponsor or its designee will issue the

determination as to whether the AE requires IND safety reporting to FDA as a serious and unexpected suspected adverse drug reaction (SUSAR). For protocols not conducted under an IND, in the event of disagreement between the reporting physician and the AMC medical monitor regarding the relationship of the AE to the investigational agent(s) (i.e., determination of whether the attribution is unrelated or unlikely, or possible, probable, or definite), the AMC medical monitor will provide the final determination of the relationship. IND safety reporting to FDA is performed by CTEP for trials conducted under a CTEP IND; IND safety reporting is performed by the sponsor or sponsor's designee (AMC ODMC or other party defined in the study agreement or TORO) for IND studies sponsored by AMC investigators or industry sponsors.

*Expedited reporting to the Institutional Review Board (IRB)*

The requirements for IRB review will be identified in the protocol section on ethical and regulatory obligations. All AMC trials initiated before September 1, 2020 and all international sites for all AMC studies are subject to local IRB review; only U.S. sites are subject to the NCI requirement to use a single IRB for protocols initiated on or after September 1, 2020. For trials subject to local IRB review, the site principal investigator is responsible for ensuring that expedited AE reports for its trial participants and any unanticipated problems that affect the local institution only are submitted to the local IRB of the reporting institution, per the local IRB's requirements for such reporting. For studies reviewed by the single IRB, the protocol chair will render a determination as to whether a SAE or other problem constitutes a trial-wide unanticipated problem that requires reporting to that IRB, in accordance with its standards of procedure.

To comply with investigator notification requirements for IND studies under 21 CFR 312.32 and 312.55, IND safety reports from all trials the AMC conducts and reports from external sponsors investigating the same agents are made available to all investigators upon receipt from the sponsor or its designee, either via the password-protected section of the AMC Operations web site (AMC trials subject to local IRB review only) or the CTSU website (U.S. trials subject to single IRB review/CTEP IND agents). The site clinical investigator responsible for the applicable AMC protocol(s) is responsible for reviewing any IND safety reports received and documenting submission to the IRB of record (if required by local policy) within the timeline defined by the Clinical Trials Monitoring Branch (CTMB) audit guidelines.

*Procedures for monitoring trial progress and pharmacovigilance*

For trials using AdvantageEDC or Advantage eClinical for clinical data entry, the AMC ODMC provides on demand tabular listings of all reported AEs and SAEs on a participant level to the protocol chair and co-chair(s) for review via the password-protected section of the AMC Operations web site, www.AIDScancer.org. For trials using OPEN and Medidata Rave for clinical data collection, data listing will be made available using that system. Summary reports of AEs by frequency and relationship to the investigational agent(s) are provided to all AMC investigators and their staff It is the responsibility of each site to provide trial-specific AE listings to their respective IRB, if required by its policies. For blinded studies, the AE and SAE listings are reviewed and tabulated without treatment assignment.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the protocol chair and also by the appropriate Scientific Working Group (SWG) during scheduled conference calls (monthly SWG calls and as required, protocol-specific monitoring conference calls). Summary

accrual, summary AE, and individual SAE reports are provided to SWG leadership and protocol chairs to monitor participant safety during these monthly calls.

The AMC medical monitor reviews listings of all reported AEs on a quarterly basis for assuring compliance with the protocol requirements for AE reporting and the identification of any safety concerns (individual AE or increased frequency/severity of expected AEs) for the agents under investigation. Findings from these reviews are communicated to the protocol chairs and all AMC investigators, and posted to the AMC Operations web site.

*Data and Safety Monitoring Board Review (DSMB) review*

The AMC has formed an independent Data and Safety Monitoring Board (DSMB) for AMC trials and for the ANCHOR Study. As required by NCI policy, the AMC requires DSMB review for all phase III randomized trials. All other clinical trials that the AMC initiates will be reviewed by the AMC ODMC and AMC Statistical Center during protocol development to issue a recommendation as to whether the study requires DSMB oversight, which will require the approval of the AMC Executive Committee. This determination will be based on the phase of the study, experimental design, risk posed by the investigational approach, extent of data available on the safety of an investigational agent, risk posed by the natural course of the health condition under research, and the categories of vulnerable populations involved. The involvement of a DSMB in reviewing an AMC protocol will be identified in each clinical protocol as approved by CTEP and, as applicable, required by the IRB of record.

Regarding the composition of the AMC DSMB, voting members usually include physicians, statisticians, an ethicist, and a patient advocate. All voting members have no other affiliation to the AMC and are appointed by the AMC Executive Committee with the approval of the OHAM Director. Nonvoting members are the AMC group statistician, the protocol statistician, an AMC ODMC staff member, two representatives (normally a clinician or statistician) from CTEP, and the grant program directors from the NCI Office of HIV and AIDS Malignancy (OHAM).

The DSMB reviews all applicable AMC studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all trials under review are prepared by the AMC group statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the DSMB charter. This report addresses specific toxicity issues and any other concerns about the conduct of the trial, as defined by the protocol plan for DSMB review. The report may contain information for the DSMB to render determinations for participant safety, early trial termination, results reporting, or continuing accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB chair to the AMC group chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The group chair or designee is then responsible for notifying the protocol chair and relevant SWG chair before the recommendations of the DSMB are carried out. In the unlikely event that the protocol chair does not concur with the DSMB, then the OHAM program directors and the NCI division director or designee must be informed of the reason for the disagreement. The protocol chair, relevant SWG chair, group chair,

DSMB chair, and NCI division director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a protocol amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, the DSMB's recommendations are provided to all AMC investigators and staff. It is each site principal investigator's responsibility for conveying this information to its local IRB as relevant for its protocol participation. For trials reviewed by a single IRB, the AMC ODMC will support notification to the IRB as required per its procedures.

*Cohort trial reviews not subject to DSMB review*

For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met based on a review of all safety data for the protocol-defined evaluation period. If applicable for phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met.

**Plans for Assuring Compliance with Requirements Regarding AE Reporting**

The protocol chair, AMC group chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with applicable regulatory and protocol requirements for AE reporting. The AMC site principal investigator certifies compliance with NCI and FDA requirements for trial conduct by signing the site subaward agreement for the grant and the AMC Adherence Statement for site membership; clinical investigators also certify compliance in completing the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration, and also for AMC IND studies sponsored by AMC investigators or industry sponsors. Protocol compliance with AE identification, assessment and reporting requirements is assessed by the AMC ODMC using several methods: 1) programmed system checks and messages to instruct the site to complete routine and/or expedited reporting when certain criteria are reported in the clinical data entry system; 2) programmed data reports provided to the protocol chairs that identify reports requiring expedited AE reporting; 3) remote review of data entry or data reports to ensure compliance with protocol and NCI AE reporting requirements; 4) AMC medical monitor review described in the section above; and, 5) routine site audits by reviewing the site's source documentation.

The clinical data entry systems used for AMC studies include the Oncology Patient Enrollment Network, OPEN for enrollment, and Medidata Rave for clinical data entry for enrolled participants; trials activated before September 1, 2020 or that involve only AMC international sites may be reported in AdvantageEDC/Advantage eClinical, a web-based data entry and enrollment system. These data entry systems are programmed to notify the site investigator, protocol chair, AMC medical monitor, and AMC ODMC via email in the event that a site reports an AE that meets expedited reporting criteria to NCI and/or FDA. Additional reporting conditions may be programmed depending on the sponsor reporting requirements of a given protocol (e.g., adverse events of special interest [AESI]). If the site does not follow with an expedited report, the AMC ODMC contacts sites to request compliance with reporting requirements. Additionally, the protocol chair, AMC ODMC, and the AMC medical monitor review reported AEs on a routine basis to identify AEs reported by sites that require expedited reporting. The protocol chair, AMC

SWG chairs, AMC group chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

For studies monitored by CTEP using the Data Mapping Utility (DMU), cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. For trials monitored by the NCI's Clinical Data Update System (CDUS), AE information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), AE information is transmitted electronically to NCI every two weeks.

**Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant**

In the event that temporary or permanent suspension of a trial, or major modification to the protocol is under consideration, the protocol chair will convene the AMC ODMC, AMC Statistical Center, and SWG chair by conference call to discuss the options. Suspension actions will also be reviewed by the AMC Executive Committee for program oversight and direct communication of the action with the OHAM program directors. For phase III trials, closure decisions are typically rendered by the AMC DSMB; if the trial in question is under AMC DSMB oversight but rendered by the AMC investigators, the AMC DSMB will be notified of the suspension and the reason. For phase I and II trials, the protocol chair also has the option of asking the DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO), with copy to OHAM Directors, when studies are temporarily or permanently closed. In the event of major trial modification, CTEP must approve all protocol amendments prior to distributing to the AMC sites.

**Plans for Assuring Data Accuracy and Protocol Compliance**

All study data for AMC clinical trials are entered directly by AMC clinical site staff into the applicable clinical data entry system for the trial. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. Submitted data entry forms are reviewed for compliance with the protocol and data entry instructions according to the AMC ODMC's standards for data quality processes. AMC ODMC staff routinely interacts with site staff to resolve any data submission problems.

In accordance with NCI guidelines, the AMC ODMC conducts audits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site principal investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a written corrective and preventative action plan to correct deficiencies. If needed, a repeat site audit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option to implement remedial action(s) for the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

## APPENDIX II: HTMCP DATA USE AND ACCESS POLICY

### Research Plan

Samples will be processed and analyzed at the GSC by high-coverage genomic and transcriptomic sequencing. The results will be analyzed will be made between tumor and normal DNA to identify the somatic changes present in the cancer tissues. These alterations include detection of chromosomal changes, such as, but not limited to, amplification (and levels), deletions, loss of heterozygosity, translocations, etc., expression profiling as well as detection of transcripts resulting from translocations and mutations, including single nucleotide variants, insertions, deletions, etc. The results from the tumors of one type will be examined for patterns of common changes, including mutations as a first step to identify the molecular changes that drive the cancer etiology. The alterations will also be analyzed within the context of biological pathways and systems biology.

### Coding of Samples

All biological materials and medical information will be coded in HTMCP. **Only the designated gatekeeper at each Institution** will keep the code key that matches the project identifying number to the personally identifiable information (http://datacenter.cit.nih.gov/interface/interface241/PIIguide.html; Note: this is applicable in the US, other countries may have different regulatory frames that must be complied with) using procedures in place and approved by the local institution. Researchers, including those who will be working with the participant samples and medical information, will not have access to any of the traditionally used identifying information about the participant. All materials submitted to the HTMCP will be labeled with a project-assigned ID.

### Storage and Release of Samples and Medical Information

The coded tissue samples will be sent to the Genome Science Center of the British Columbia Cancer Agency (BC-GSC), which is the characterization center for the HTMCP. The samples will be processed there and the molecular analytes extracted from samples will be used for sequencing. Any remaining samples will be stored at the BC-GSC until the end of the project. At the end of the project, any remaining samples will be handled in accordance with the protocol of contributing institution as designated in the disposition form.

Data stripped of identifiers, in compliance with the definition specified in the HIPAA Limited Data Set definition (http://hipaa.wisc.edu/ResearchGuide/limiteddatasets.html), will be submitted by the contributing institution to the Data Coordinating Center (DCC). The DCC serves as a central HTMCP project database. The DCC also stores the molecular profiling data generated with the DNA and RNA.

### Data Access

- Information (data) from analyses of the coded samples and the coded medical information will be deposited into publicly available databases. These databases will be accessible by the Internet. Medical information and molecular characterization results on the coded samples will be stored in a controlled-access database. The information in this database will be available only to researchers have received approval from the NCI Data Access Committee after their institutions have certified their adherence to participant data protection policies for the project

(http://epi.grants.cancer.gov/dac/charter.html).

- To ensure protection of genetic privacy for sample donors, data users will have to agree to certain conditions described in the HTMCP Patient Protection Policy and Controlled Access Policy as to how the data will be used. For example, users will have to agree that they will share these data only with others who have also completed a data access agreement and that they will not patent discoveries in a way that prevents others from using the data. This means that reviewers of a manuscript who need to see any controlled-access HTMCP data underlying a result must also agree to these user access conditions before they can see these data.
- Anonymous information from the analyses will be put in a public database, available to anyone on the Internet.

## APPENDIX III: PROCESSING BLOOD SAMPLES FOR THE HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT

(HTMCP SOP#206, Version 4.0)

# I. INTRODUCTION

## A. Scope and Purpose

1. To establish a common procedure for blood processing prior to shipment to the AMC Biorepository.
2. This protocol applies to all AMC sites providing tissues prospectively. AMC sites are also permitted to prepare PBMC aliquots according to the ACSR's SOP, Separation of Plasma and Mononuclear Cells, available on the AMC Operations web site (www.AIDSCancer.org).
3. Any deviation from this SOP should be noted in the lab notebook, indicating nature of deviation, times and which samples were affected. This information should be given within 48 hours of the occurrence to the Project Team (PT) representative by sending an email to ocg@nih.nci.gov with the details.

## B. Safety Precautions

1. Wear personal protective equipment (PPE) such as lab coats and gloves.
2. Liquid nitrogen is extremely cold and can cause 'burns.' Wear gloves that are specially made to withstand liquid nitrogen, eye protection (preferably Face Shield), and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; be sure to use in a well-ventilated area.

## C. Equipment and Materials

1. Personal protective equipment (PPE) to include latex or nitrile gloves, heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
2. Clinical Centrifuge with swinging bucket rotor
3. 250 mL flask containing 50 mL bleach for waste disposal
4. Cryovials (e.g., 2mL screw cap vials from ChartBiomed, Part Number 10778828)
5. GlobalTrace labels
6. Dewar thermo-flask 1L
7. Liquid nitrogen
8. Isopentane (2 methyl butane, certified grade)
9. Three-prong beaker tongs
10. PBMC separation tube
11. Disposable transfer pipette
12. 100 mL metal beaker

13. Long forceps, 8-12”
14. Timer
15. Fine point Cryomarker
16. Disposable, sterile plastic transfer pipettes or sterilized glass Pasteur pipettes
17. Ice bucket
18. Dry ice

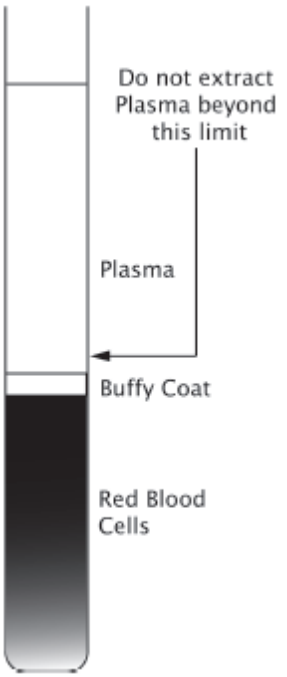
## II. PROCEDURE

### A. Collection

1. Collect 10 mL of blood in a tube containing either EDTA or acid citrate dextrose (ACD) anticoagulant.
2. Prepare an ice bucket with dry ice. Chill one 2mL cryovial to collect the white blood cells isolated in the procedure. The vial must be identified with a GlobalTrace label.

### B. Blood Separation

1. Fractionate the whole blood by centrifuging at 1500-2000 *X* g for 10-15 min at room temperature. This will separate the blood into an upper plasma layer, a lower red blood cell (RBC) layer, and a thin interface containing the white blood cells (WBCs) / buffy coat (see Figure 1). Fractionate the blood as soon as possible after collection.
   **NOTE:** In a typical clinical centrifuge 1500-2000 *X* g is ~3000-3400 rpm. Check the appropriate settings for your centrifuge using the nomogram in your user’s manual.




2. Use a disposable plastic transfer pipet or Pasteur pipet to slowly and carefully aspirate the plasma (upper layer) down to about 1 mm above the buffy coat. Do not disturb the buffy coat. Discard the plasma into a 250 mL flask containing bleach.
3. Gently recover the buffy coat (WBCs) with a fresh disposable pipet, Pasteur pipet, or 1000 µl micropipettor with a sterile tip. Try not to uptake the RBC layer below the buffy coat.
4. Place the recovered buffy coat into the WBC labeled cryovial cooled on ice from step 2.
5. Screw on the cryovial cap **tightly** to prevent isopentane from seeping into the vial.
6. Visually estimate the volume of WBCs recovered using the volume lines on the cryovial and write the information into the datasheet. Buffy coat volume is greater in samples with high WBC counts. Usually you can expect ≤ 0.5 mL total.
7. Proceed to section C, “Freezing Collected Cells.”

## C. Freezing Collected Cells

1. Set Up Freezing Station
    - Do not perform snap freezing with bare hands. Wear gloves at all times and heavy duty gloves when working with liquid nitrogen or cooled isopentane.
    - Use extreme caution when dispensing liquid nitrogen.
        - Fill a small 100 mL metal beaker about 1/4 full with isopentane.
        - Fill the Dewar thermo-flask about 1/3 full with liquid nitrogen.
2. Freezing Cells in Cryovials
    - Using beaker tongs lower the 100 mL metal beaker containing isopentane half-way into the liquid nitrogen for cooling. The liquid nitrogen will boil as the beaker is lowered. When the isopentane is reaching its freezing point the tone of the boiling will increase for 2-3 seconds.
    - Using beaker tongs, lift the beaker out of the liquid nitrogen once you see beads of solid isopentane at the bottom of the beaker (about 2 minutes). Place the beaker on the workbench.
    - Use long forceps to hold one to three cryovial(s) down into the cooled isopentane. Submerge cryovial(s) for at least 1 minute.
    - Take out the cryovial(s) containing frozen tissue.
    - Store frozen cryovial(s) in liquid nitrogen storage tanks or -80°C freezers.

**THE FROZEN SPECIMENS SHOULD BE KEPT FROZEN ON DRY ICE AT ALL TIMES DURING TRANSPORT TO AND FROM STORAGE TANKS**.

## APPENDIX IV: SHIPPING INSTRUCTIONS FOR SUBMITTING PBMC, SNAP FROZEN BIOPSY TISSUE, AND FORMALIN-FIXED TISSUE TO THE AMC BIOREPOSITORY

### A. GENERAL

- It is the responsibility of the Primary Investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations (IATA Packing Instruction 650) relating to the handling and shipping of hazardous goods. (IATA Packing Instruction 650 is located on the AMC website.)
- Use a federally approved shipper for biological substance shipment (Category B). Label the shipper with the "Infectious substance" diamond-shaped label. On one side, in black marker write “Biological Substance, Category B, [redacted] your name or name of responsible person, date of collection, and phone number of the person responsible for the package. Package and label the shipment in accordance with the instructions provided for that specific shipper.
- A Shipper’s Declaration for Dangerous Goods is not required. However, for all dry ice shipments, the following information must be shown in sequence on the airway bill in the “Nature and Quality of Goods” box: Dry Ice, Class 9, [redacted] number of boxes being shipped, net weight of dry ice per box.

  **NOTE:** Specimens MUST BE SHIPPED **Monday** through **Thursday** as a **PRIORITY OVERNIGHT** shipment. Specimens are **NOT ACCEPTED ON SATURDAYS OR SUNDAYS** in the AMC Biorepository.

### B. SPECIMEN PACKAGING AND SHIPMENT

*Specimen Labeling for PBMC and All Tissue Samples*

This study will use both HTMCP specimen IDs and GlobalTrace labels during the screening process**.**

With a black, water resistant, sharpie pen, label each GlobalTrace specimen label with the following information:

- AMC Protocol #: AMC-083
- AMC Subject ID#
- Date and time of collection
- Specimen type, i.e., PBMC, Fresh Frozen Biopsy, Tissue (block), Tissue (scrolls or H&E slides), Tissue (unstained slide)
- Specimen purpose: Genomic Sequence Analysis, Central Pathology Review

*Shipment Preparation for PBMC Samples*

Reference Appendix III for the preparation of PBMC samples.

- PBMC specimens should be shipped by overnight express on dry ice. Approximately 2 kg (4.4 lbs.) of dry ice pellets or chunks are needed for packaging samples.

- Specimens must be shipped on dry ice in a Styrofoam box, and then shipped in an outer cardboard box (required by FedEx).
- Affix the FedEx airbill on blank side of the shipper making sure that it is marked "FedEx PRIORITY OVERNIGHT."
- Mark "OTHER" in the airbill under "Packaging." Please refer to the Manual of Procedures and the AMC Operations website's (www.AIDSCancer.org) Shipping tab for more information and the FedEx account details.
- Under airbill section "Special Handling" indicate "YES-SHIPPERS DECLARATION NOT REQUIRED."
- Place "From/To" information onto areas provided on the shipper.
- Make certain that shipper is already either pre-labeled with [redacted] stamp, or make a paper label with [redacted] and affix it to the shipper.
- Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in ml and affix to the shipper.
- Affix airbill to shipper so that the 'UN' and 'VOLUME' labels are visible.
- RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
- Place the box in the FedEx pickup area at your site or call to request a package pickup.

  **Please Note:** The shippers will be mailed back to each AMC site.

  *****PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.**

*Preparation of Snap Frozen Biopsy Tissue Samples for Shipment*

Tissue specimens to be fresh frozen should be placed in histowrap and then on dry ice immediately. The specimens may stay on dry ice until being transferred to a -80ºC freezer.

Tissue specimens for donation may be batched for shipping after storage in -80ºC freezer.

*NOTE: Specimens can only be accepted **Monday through Friday**. Therefore, specimens can only be shipped **Sunday-Thursday** for delivery the next day. Shipping frozen tissue requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

*Preparation of FFPE Tissue Block, Scrolls, or Slides for Shipment*

- Place the labeled tissue block or slides into a specimen container in bubble wrap or other adequate cushioning. Use sturdy outer packaging to prevent breakage.
- Affix the FedEx airbill on blank side of the shipper.
- Mark "OTHER" in the airbill under "Packaging."

- Under airbill section "Special Handling" indicate "YES-SHIPPERS DECLARATION NOT REQUIRED."
- Please refer to the Manual of Procedures and the AMC Operations website's (www.AIDSCancer.org) Shipping tab for the FedEx account details. Place "From/To" information onto areas provided on the shipper. Specimens are accepted MONDAY through THURSDAY only. FFPE tissue and slides should be shipped at ambient temperature by **FedEx 2-day service** to Dr. Silver at the address listed below. **The tissue scrolls must be sent from the site to British Columbia Cancer Agency (BCCA) priority overnight (see item 6 below).**
- Make certain that shipper is visibly labeled "Exempt human specimen."
- RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
- Place the box in the FedEx pickup area at your site or call to request a package pickup.

*PBMC, FFPE block specimens, and pathology slides should be shipped to*:

Dr. Sylvia Silver
George Washington University Medical Center
2300 I Street, NW
Ross Hall, Room 118
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@email.gwu.edu

**Technical Questions**

Contact Dr. Silver as noted above, or
Razan Humeida (rhumeida@gwmail.gwu.edu, 202-994-3422), or
Jonathan Lang (jlang13@gwmail.gwu.edu, 202-994-3422), or
Sarah Fukui (sfukui@gwmail.gwu.edu, 202-994-3422)

*Preparation and Shipment of FFPE Tissue Scrolls*

**In the absence of frozen tumor tissue, an FFPE block may be shipped to the BCCA following notification from the program office. If an FFPE block cannot be shipped, the following tissue scroll procedure can be used.**

- ***Cut a 4 µm slice and stain the slide with H&E stain as a top stain for pathology review***
- Measure length and width (in mm) of tissue specimen surface within paraffin block (see figure below)
- Double click on excel table provided by the program office (available on AMC Operations web site among the AMC-083 protocol materials) to open editing function. (www.AIDSCancer.org)
- Enter tumor length and width values measured in step b and cut the number of 10 micrometer scrolls required to create $12mm^3$ is shown in yellow

- Put scrolls in tube for shipping (Eppendorf or cryovial)
- ***Cut a 4 µm top slide and stain with H&E stain as a bottom slide for pathology review***

  Ship tube of scrolls and the two H&E stained slides immediately to the BCCA at ambient temperature within 24 hours of cutting scrolls, via priority overnight service (with cold pack April-September). The BCCA must be informed of a shipment via email at least one day before shipment at the following email address: GSC_Submissions@bcgsc.ca

  BCCA Contact Information
  Biospecimen Administrator
  Cc: Dr. Andrew J. Mungall
  Genome Sciences Centre
  British Columbia Cancer Agency
  Suite 100
  570 W. 7th Avenue
  Vancouver, BC V5Z 4S6
  CANADA
  Phone: (604) 877-6088
  Email: GSC_Submissions@bcgsc.ca

## C. BILLING

Please refer to the Manual of Procedures and the AMC Operations website's (www.AIDSCancer.org) Shipping tab for the FedEx account details. It is only to be used for billing shipment of specimens to the lab where the sample is processed and/or stored.

## D. RECORD OF SPECIMENS

This study will track specimens via GlobalTrace, a component of the AMC AdvantageEDC system. The GlobalTrace shipment manifest must accompany all specimen shipments.

## APPENDIX V: PERFORMANCE STATUS SCALES

| Karnofsky Performance Scale | | ECOG Performance Status Scale | |
|---|---|---|---|
| **Percent** | **Description** | **Grade** | **Description** |
| 100 | Normal, no complaints, no evidence of disease. | 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease. | | |
| 80 | Normal activity with effort; some signs or symptoms of disease. | 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 70 | Cares for self, unable to carry on normal activity or to do active work. | | |
| 60 | Requires occasional assistance, but is able to care for most of his/her needs. | 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 50 | Requires considerable assistance and frequent medical care. | | |
| 40 | Disabled, requires special care and assistance. | 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 30 | Severely disabled, hospitalization indicated. Death not imminent. | | |
| 20 | Very sick, hospitalization indicated. Death not imminent. | 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 10 | Moribund, fatal processes progressing rapidly. | | |
| 0 | Dead. | 5 | Dead. |