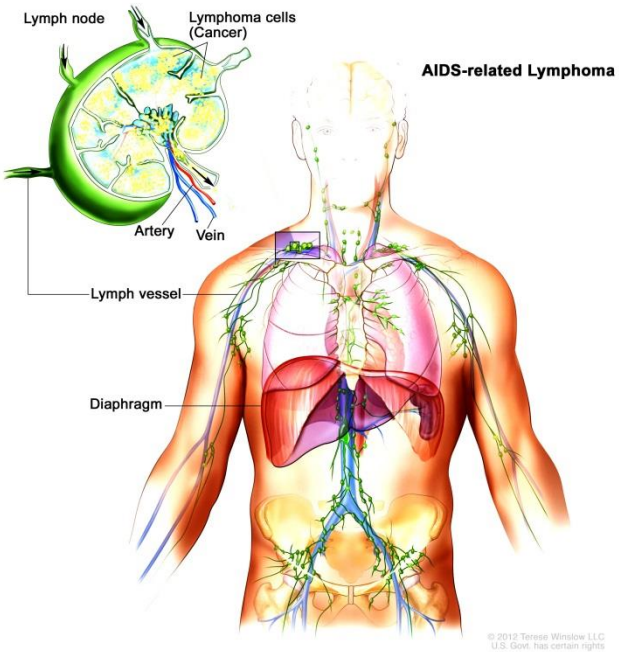
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Aids-related Lymphoma

Introduction

The term 'Aids-related lymphoma' describes those lymphomas occurring in individuals with Acquired Immune-deficiency Syndrome (Aids).



[Picture Credit: Aids-related Lymphoma]

A lymphoma is a type of cancer that arises from lymphoid cells. In Aids, the incidence of non-Hodgkin's lymphoma, primary cerebral lymphoma and Hodgkin's lymphoma are all increased.

There are three (3) different varieties of Aids-related lymphoma: Diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, and small non-cleaved cell lymphoma (Burkitt's lymphoma). (Wikipedia).

The lymph system is made up of thin tubes that branch, like blood vessels, into all parts of the body. Lymph vessels carry lymph, a colourless, watery fluid that contains white blood cells called lymphocytes back into the bloodstream. Along the network of vessels are groups of small, bean-shaped organs called lymph nodes through which the lymph travel on their way back into the bloodstream.

Clusters of lymph nodes make, and store, infection-fighting cells. The spleen is an organ in the left upper abdomen that makes lymphocytes and filters old blood cells from the blood. Other lymph tissue includes the thymus, a small organ beneath the breastbone, and the tonsils, organs in the throat. They are all part of the lymphatic system.

Because there is lymph tissue in many parts of the body, the cancer can spread to almost any of the body's organs or tissues including the liver, bone marrow (spongy tissue inside the large bones of the body that makes blood cells), spleen or brain.
(University of California San Francisco).

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Key Points Regarding Aids-related Lymphoma (ARL)
Important key points of Aids-related lymphoma (ARL) include:

- Aids-related lymphoma is a disease in which malignant (cancer) cells form in the lymph system of patients who have acquired immunodeficiency syndrome (Aids)
- There are many different types of lymphoma
- Aids-related lymphomas grow and spread quickly
- Signs of Aids-related lymphoma include weight loss, fever, and night sweats
- Tests that examine the body and lymph system are used to help detect (find) and diagnose Aids-related lymphoma
- Certain factors affect prognosis (chance of recovery) and treatment options

(National Cancer Institute).

Incidence of Aids-related Lymphoma in South Africa
The National Cancer Registry (2013) does not provide any statistics regarding the incidence of Aids-related Lymphoma. According to the National Cancer Registry (2012) the following number of Burkitt's Lymphoma cases were histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	73	1:4 276	0,20%
Asian males	1	1:6 320	0,13%
Black males	57	1:4 153	0,53%
Coloured males	5	1:7 731	0,12%
White males	9	1:3 092	0,05%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	72	1:4 927	0,20%
Asian females	0	-	-
Black females	59	1:4 497	0,38%
Coloured females	6	1:6 270	0,15%
White females	7	1:4 068	0,04%

The frequency of histologically diagnosed cases of Burkitt's Lymphoma in South Africa for 2013 were as follows (National Cancer Registry, 2013):

Group - Males 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	16	3	21	21	10	2	0	0
Asian males	0	0	0	0	1	0	0	0
Black males	10	1	14	19	8	1	0	01
Coloured males	2	1	2	0	0	0	0	0
White males	2	0	3	2	1	1	0	0

Group - Females 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	9	7	27	19	8	1	0	0
Asian females	0	0	0	0	0	0	0	0
Black females	5	5	23	15	8	1	0	0
Coloured females	2	1	1	2	0	0	0	0
White females	2	1	2	2	0	0	0	0

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

According to the National Cancer Registry (2013) the following number of Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	273	1:994	0,76%
Asian males	11	1:809	1,36%
Black males	170	1:1 433	1,58%
Coloured males	34	1:804	0,81%
White males	59	1:468	0,29%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	184	1:1 848	0,50%
Asian females	10	1:809	0,92%
Black females	121	1:2 314	0,77%
Coloured females	19	1:1 996	0,47%
White females	35	1:827	0,22%

The frequency of histologically diagnosed cases of Hodgkin's Lymphoma in South Africa for 2013 were as follows (National Cancer Registry, 2013):

Group - Males 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	47	48	62	50	35	17	8	1
Asian males	0	1	3	2	2	2	0	1
Black males	31	33	42	33	19	5	0	0
Coloured males	7	3	6	7	6	1	1	0
White males	7	10	10	6	8	9	6	0

Group - Females 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	18	48	53	34	16	9	4	0
Asian females	1	0	4	1	1	2	0	0
Black females	9	32	36	24	10	3	0	0
Coloured females	3	4	5	2	3	0	1	0
White females	5	9	7	5	1	3	3	0

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

According to the National Cancer Registry (2013) the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	882	1:221	2,45%
Asian males	25	1:241	2,97%
Black males	516	1:316	4,79%
Coloured males	88	1:192	2,12%
White males	254	1:123	1,26%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	802	1:327	2,19%
Asian females	21	1:296	1,98%
Black females	471	1:461	3,02%
Coloured females	76	1:267	1,87%
White females	234	1:163	1,47%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2013 was as follows (National Cancer Registry, 2013):

Group - Males 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	29	46	152	199	172	144	85	40
Asian males	0	0	1	7	7	5	2	1
Black males	25	30	126	142	105	40	18	5
Coloured males	2	4	7	14	18	27	8	4
White males	2	9	15	32	38	67	55	28

Group - Females 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	24	54	164	165	124	125	81	52
Asian females	1	0	0	3	2	7	4	1
Black females	16	47	140	122	61	39	16	10
Coloured females	2	3	10	12	18	13	11	4
White females	5	2	12	23	38	60	48	36

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Background and Pathophysiology to Aids-related Lymphomas (ARL)

Individuals infected with human immunodeficiency virus (HIV) have a high risk of developing lymphomas. Approximately 4% of people with Acquired Immunodeficiency Syndrome (Aids) have non-Hodgkin's Lymphoma (NHL) at diagnosis and at least the same proportion develop NHL during the course of illness.

Human immunodeficiency virus (HIV) infection results in impaired cellular immunity, a condition known to predispose persons to develop neoplasms. As the lifespan of HIV-infected patients has increased, malignancies have become a known cause of morbidity and mortality in this population. Before the advent of antiretroviral therapy (ART), malignancies accounted for approximately 10 percent of HIV-related deaths. Since the routine implementation of ART, a cancer diagnosis is made in over 40 percent of HIV-infected patients during the course of the HIV infection [5], and over 28 percent of HIV-related deaths are attributable to malignancy.

There are three acquired immune deficiency syndrome (AIDS)-defining malignancies: Kaposi sarcoma, non-Hodgkin lymphoma (NHL) of high-grade pathologic type and of B cell or unknown immunologic phenotype, and invasive cervical carcinoma. In addition, non-AIDS-defining malignancies contribute to mortality in HIV-infected persons.

The treatment options in these patients have unique challenges, and although the prognosis is improving, it still remains poor.

Since the start of the Aids pandemic in the early 1980s, the disease has been a focus of researchers worldwide. Various tumours related to Aids have been identified and their mysteries unveiled. Aids-related lymphomas (ARLs) are no exception. Most ARLs are high-grade, aggressive NHLs.

The aetiology (cause) of NHL is largely unknown; however, several factors play an important role in development of the disease. These include infections with viruses, namely Epstein-

Barr virus infection and human herpesvirus 8 (HHV-8) infection; continuous B-cell stimulation; and last, but not least, immunodeficiency.

Different clinicopathologic categories of Aids-related lymphomas (ARLs) arise from distinct B-cell subtypes, and the factors mentioned above interplay in varying proportions to give rise to different varieties of NHL.
(UpToDate).

Systemic non-Hodgkin's Lymphoma (NHL) - systemically arising NHL constitutes about 80% of all AIDS-related lymphomas (ARLs). These lymphomas are of the following varieties:

- Small, noncleaved cell lymphoma, including Burkitt's lymphoma and Burkitt-like lymphoma
- Diffuse, large cell lymphoma, including centroblastic lymphoma, immunoblastic lymphoma, and plasmablastic lymphoma of the oral cavity.

NHLs are heterogeneous in their molecular pathogenesis. Activation of c-myc occurs in all Aids patients with Burkitt's lymphoma. Inactivation of p53 is found in 50-60% of patients and EBV infection in 30-50%.

In centroblastic NHL, Epstein-Barr V infection is found in 30% of affected individuals. BCL-6 proto-oncogene is positive in 20% of patients.

EBV is positive in 90% of patients with immunoblastic lymphoma, and latent membrane protein (LMP)-1 (EBV-encoded protein) is expressed in 65-75% of patients. Epstein Barr Virus-positive lymphomas express LMP1, suggesting a pathogenic role of the virus in development of lymphomas. LMP1 is positive only in immunoblastic lymphomas.

In plasmablastic lymphoma of the oral cavity, the malignant cells tend to grow in a cohesive manner. The cells are usually large, monomorphic, and have abundant cytoplasm with a peripherally placed nucleus. There is a single prominent nucleolus.

Differentiating plasmablastic lymphoma from immunoblastic lymphoma is possible by appreciating the differences in morphology (shape and structure), with the immunoblastic variety being polymorphic and more heterogeneous. Epstein-Barr Virus infection is present in 50% of the patients with plasmablastic lymphoma of the oral cavity.

Primary Effusion Lymphoma - HHV-8 is present in all patients with primary effusion lymphoma. Coinfection with Epstein-Barr Virus is present in 90-100% of the cases. c-Myc activation is not present, and rearrangements in the coding region of BCL proto-oncogenes are not found.

Primary CNS Lymphoma - PCNSLs generally have immunoblastic histology. There is consistent infection of the tumour cells by Epstein-Barr Virus, with 90% of the patients expressing LMP-1, suggesting the importance of the virus in the pathogenesis (causation) of the tumour. Most of the patients have mutations of BCL-6, and they also express high levels of the BCL-2 protein. Continuous B-cell stimulation plays an important role in development of these tumours.

(Medscape; Canadian Cancer Society).

Symptoms of Aids-related Lymphoma (ARL)

The symptoms of Aids-related Lymphoma is often similar to that of non-Hodgkin's lymphoma and can be vague. These are common symptoms:

- Fever
- Night sweats
- Weight loss
- Fatigue
- Swelling in lymph nodes in your neck, underarm, groin, or stomach
- Skin rash or itchy skin
- Pain in the chest, abdomen, or bones

(Canadian Cancer Society).

Diagnosis of Aids-related Lymphoma (ARL)

Various tests are used to diagnose Aids-related lymphoma, identify the type of lymphoma present, and determine how fast it is growing. These tests can also indicate whether the condition has spread, how well it may respond to therapy, and whether it is likely to return.

Blood Tests to Diagnose HIV - Doctors may use several blood tests to diagnose HIV Infection and gauge the health of the immune system, especially if the patient has not already been diagnosed with HIV. A basic HIV blood test determines whether the patient has developed antibodies to HIV. People with Aids-related lymphoma often have high levels of these antibodies in their blood at the time of diagnosis.

Blood tests also measure viral load, which reveals how many virus cells the patient is carrying, and the number of CD4 cells. People with Aids-related lymphoma who have not been taking antiretroviral medication often have an increased viral load and a lowered CD4 count. As the number of CD4 cells decreases, the immune system becomes progressively impaired.

Lymph Node Biopsy - a lymph node biopsy can confirm a diagnosis of Aids-related lymphoma and identify the type of lymphoma the patient has. This procedure involves removing tissue from a swollen lymph node and evaluating it under a microscope. The tissue sample also may be used to look for genetic mutations associated with some non-Hodgkin's lymphomas. This information can help the doctor to select the most effective treatment.

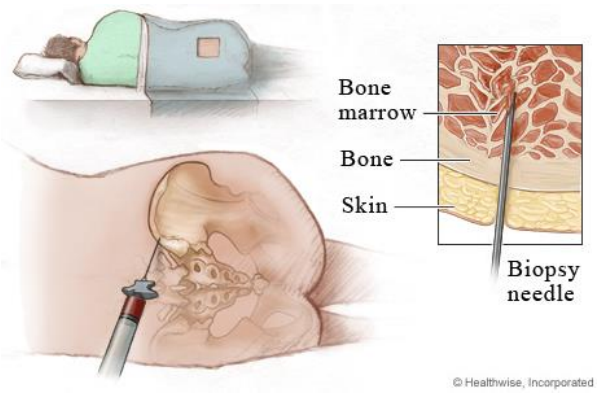
Surgical Biopsy - surgeons usually remove an entire lymph node to perform a biopsy. Surgical biopsy is performed in the hospital using local anaesthesia. Most people go home the same day.

Needle Biopsy - sometimes, a surgical biopsy is not possible because a swollen lymph node is difficult to reach without harming blood vessels or other structures. The doctor may perform a needle biopsy, using fine needle aspiration or core needle biopsy, to obtain a tissue sample.

In fine needle aspiration, the doctor uses a small, thin needle to withdraw fluid and cells from an enlarged lymph node. In a core needle biopsy, the doctor uses a bigger needle to remove a larger portion of tissue. Both types of needle biopsy are performed as outpatient procedures using a local anaesthetic.

If the lymph node is located deep within the body, the doctor may use an imaging technique to help guide the needle before inserting it. Depending on the location of the lymph node, the doctor may use a CT scan - a type of X-ray - or an ultrasound, in which sound waves produce images of structures in the body.

Bone Marrow Aspiration and Biopsy - the doctor may recommend a bone marrow aspiration and biopsy to determine if lymphoma has spread to the bone marrow.



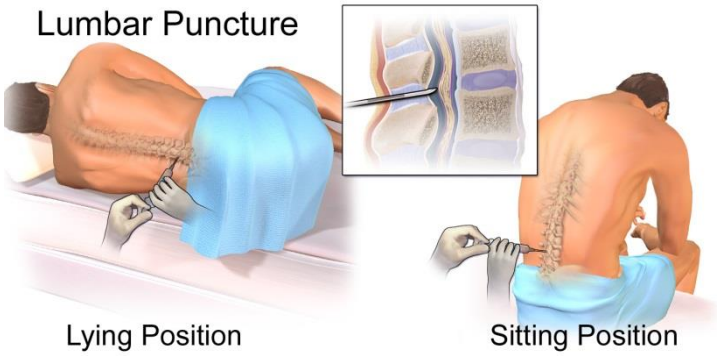
[Picture Credit: Bone Marrow Aspiration and Biopsy]

During a bone marrow aspiration, the doctor uses a needle to withdraw liquid and tissue from bone marrow in the back of the pelvis. To perform a biopsy, he or she removes a tiny piece of bone, about half the size of a matchstick, from the same area. New bone quickly regrows, replacing the piece that has been removed. Tissue samples are evaluated under a microscope to look for lymphoma cells.

Both of these procedures require a local anaesthetic and may be conducted in the doctor's consulting rooms or in the hospital as an outpatient procedure.

Lumbar Puncture - doctors may perform a lumbar puncture, also known as a spinal tap. This test, performed on an outpatient basis in the hospital, can reveal whether lymphoma has spread to the cerebrospinal fluid, a liquid that cushions the spine and brain.

In this test, the doctor injects a local anaesthetic into the skin in the lower back. Then, he or she inserts a hollow needle into the spinal canal to remove a small amount of cerebrospinal fluid. Doctors examine the fluid under a microscope to look for the presence of lymphoma cells.



[Picture Credit: Lumbar Puncture]

Imaging Tests - doctors may also use imaging tests to determine how far the cancer has spread and how quickly it is growing.

CT Scans - a CT scan uses X-rays and a computer to create three-dimensional, cross-sectional images of the body. This test can help the doctor identify the location of a tumour and measure its size.

Before this scan, the doctor may administer a contrast material, or dye, by injection or by mouth, as a liquid or a pill. The dye helps to highlight images of the tumour and surrounding blood vessels on the scan. It contains iodine, so it is not recommended for anyone with an allergy to iodine.

PET Scans - the doctor may use a PET scan to look for smaller Aids-related non-Hodgkin's lymphoma tumours and to determine how active the disease is - that is, how quickly the cells are processing glucose, or sugar.

During a PET scan, the doctor injects a small amount of radioactive glucose into a vein. This substance collects in tumour cells, which are detected by a computer during the scan. The computer then creates three-dimensional images of cancer activity in the body.

Additional Blood Tests - if one has been diagnosed with Aids-related lymphoma, the doctor may order additional blood tests to determine if the patient has anaemia - a reduction in oxygen-carrying red blood cells - or a low number of platelets, which help the blood to clot. Another blood test measures the level of an enzyme called lactate dehydrogenase, which often increases as lymphoma advances.

Blood tests may also be used to look for infection with Epstein-Barr Virus. This virus causes mononucleosis, commonly known as 'mono', and increases the risk of developing Hodgkin lymphoma in people who have HIV, as well as those who do not.
(NYU Langone Medical Center).

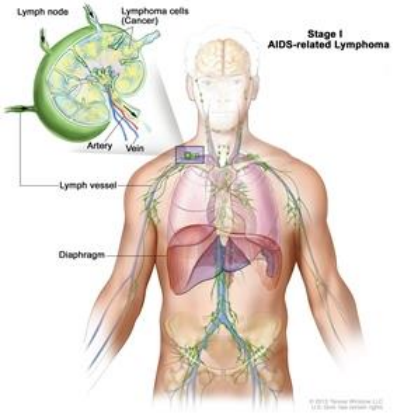
Staging of Aids-related Lymphoma (ARL)
Staging of Aids-related lymphoma may be described as follows:

- E: "E" stands for extranodal and means the cancer is found in an area or organ other than the lymph nodes or has spread to tissues beyond, but near, the major lymphatic areas.

- S: "S" stands for spleen and means the cancer is found in the spleen.

The following stages are used for Aids-related lymphoma:

Stage I



Stage I Aids-related lymphoma. Cancer is found in one lymphatic area (lymph nodes, tonsils, thymus, or spleen). In stage IE (not shown), cancer is found in one organ or area outside the lymph nodes.

Stage I Aids-related lymphoma is divided into stage I and stage IE.

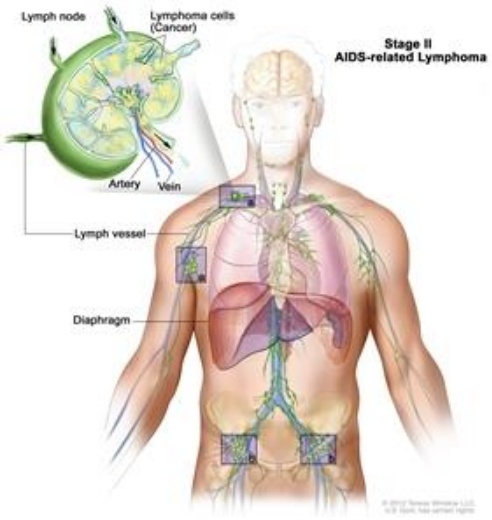
Stage I: Cancer is found in one lymphatic area (lymph node group, tonsils and nearby tissue, thymus, or spleen).

Stage IE: Cancer is found in one organ or area outside the lymph nodes.

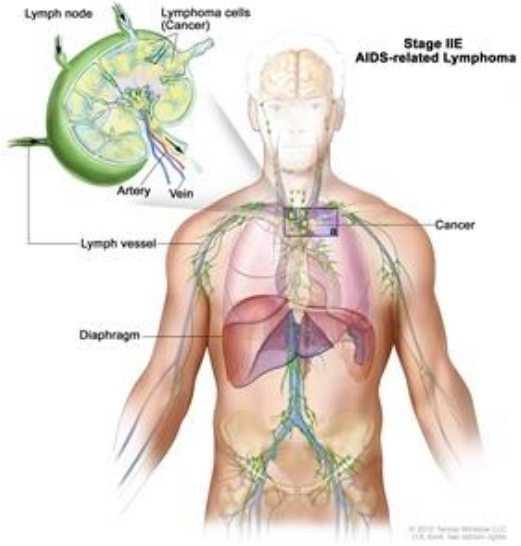
Stage II

Stage II Aids-related lymphoma is divided into stage II and stage IIE.

- Stage II: Cancer is found in two or more lymph node groups either above or below the diaphragm (the thin muscle below the lungs that helps breathing and separates the chest from the abdomen)

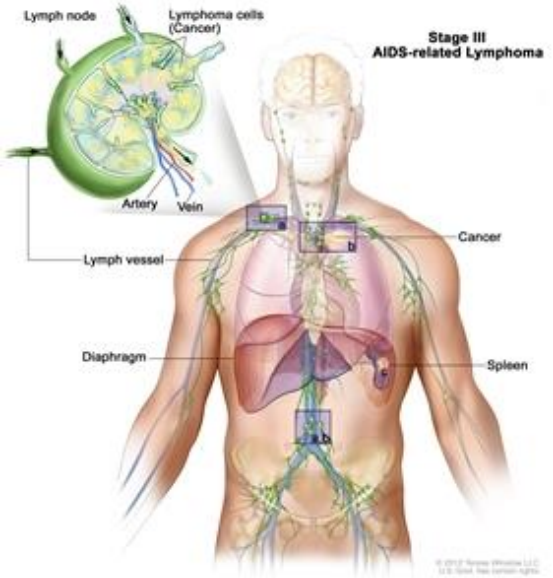


Stage II Aids-related lymphoma. Cancer is found in two or more lymph node groups, and both are either above (a) or below (b) the diaphragm.



- Stage IIE: Cancer is found in one or more lymph node groups either above or below the diaphragm. Cancer is also found outside the lymph nodes in one organ or area on the same side of the diaphragm as the affected lymph nodes.

Stage IIE AIDS-related lymphoma. Cancer is found in one or more lymph node groups either above or below the diaphragm and outside the lymph nodes in an organ or area on the same side of the diaphragm as the lymph nodes with cancer (a).



Stage III

Stage III Aids-related lymphoma. Cancer is found in one or more lymph node groups above and below the diaphragm (a). In stage IIIE, cancer is found in lymph node groups above and below the diaphragm and outside the lymph nodes in a nearby organ or area (b). In stage IIIS, cancer is found in lymph node groups above and below the diaphragm (a) and in the spleen (c). In stage IIIE plus S, cancer is found in lymph node groups above and below

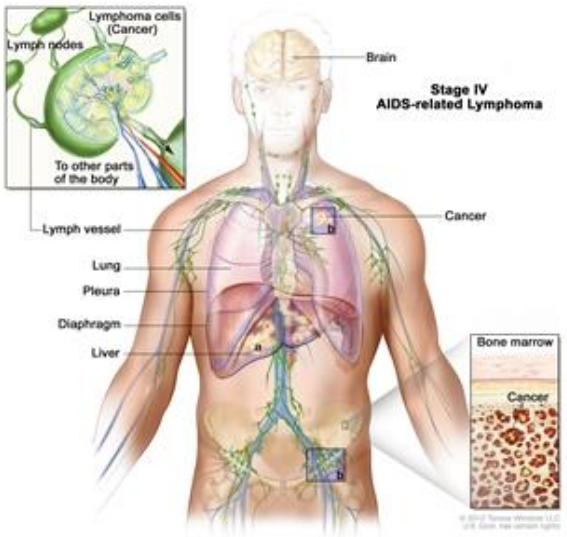
the diaphragm, outside the lymph nodes in a nearby organ or area (b), and in the spleen (c).

Stage III Aids-related lymphoma is divided into stage III, stage IIIE, stage IIIS, and stage IIIE+S.

- Stage III: Cancer is found in lymph node groups above and below the diaphragm (the thin muscle below the lungs that helps breathing and separates the chest from the abdomen).
- Stage IIIE: Cancer is found in lymph node groups above and below the diaphragm and outside the lymph nodes in a nearby organ or area.
- Stage IIIS: Cancer is found in lymph node groups above and below the diaphragm, and in the spleen.
- Stage IIIE+S: Cancer is found in lymph node groups above and below the diaphragm, outside the lymph nodes in a nearby organ or area, and in the spleen.

Stage IV

Stage IV Aids-related lymphoma. Cancer is found throughout one or more organs that are not part of a lymphatic area (lymph nodes, tonsils, thymus, or spleen) (a); or in one organ that is not part of a lymphatic area and has spread to lymph nodes far away from that organ (b); or cerebrospinal fluid (not shown), the liver, bone marrow, or lungs.



In stage IV Aids-related lymphoma, the cancer:

- is found throughout one or more organs that are not part of a lymphatic area (lymph node group, tonsils and nearby tissue, thymus, or spleen) and may be in lymph nodes near those organs; or
- is found in one organ that is not part of a lymphatic area and has spread to organs or lymph nodes far away from that organ; or
- is found in the liver, bone marrow, cerebrospinal fluid (CSF), or lungs (other than cancer that has spread to the lungs from nearby areas).

(WebMD).

Treatment of Aids-related Lymphoma (ARL)

Treating Aids-related lymphoma is usually a combination of treating the lymphoma and treating Aids. Generally, an Aids-related lymphoma is harder to treat than a lymphoma not related to Aids.

Different treatments and combinations of treatment may be used to treat Aids-related lymphoma.

HAART - highly active antiretroviral therapy (HAART) is used to slow down the progression of Aids. People with Aids have weakened immune systems and cancer treatment can cause

more problems. As a result, people with Aids-related lymphoma are sometimes treated with lower doses of chemotherapy drugs than people with lymphoma who do not have Aids.
Treatment with HAART may allow some people with Aids-related lymphoma to safely receive combinations of chemotherapy drugs in standard or even higher doses. When colony-stimulating (hematopoietic) growth factors are added to chemotherapy, people can tolerate treatment better.

Chemotherapy - combinations of chemotherapy drugs, which are used to treat other aggressive B-cell types of lymphoma, are often used to treat Aids-related lymphoma. Some of these combinations include CHOP or CHOP-like therapies.

- CHOP – cyclophosphamide (Cytoxan, Procytox), doxorubicin (Adriamycin), vincristine (Oncovin) and prednisone (Deltasone)
- CDE – cyclophosphamide, doxorubicin and etoposide (Vepesid, VP-16)
- EPOCH – etoposide, doxorubicin, vincristine, cyclophosphamide and prednisone

Biological therapy - the use of monoclonal antibodies, such as rituximab (Rituxan), is not well-defined in Aids-related lymphomas because of the increased risk of infection in people with Aids. However, it may be used in combination with chemotherapy in people with high enough CD4 counts.

Drugs to prevent and treat infections - drugs, such as antibiotics, are also used to prevent and treat infections.

Colony-stimulating factors - colony-stimulating factors (CSFs) are used to stimulate the bone marrow to produce more of certain blood cells. This helps reduce the risk of infection, anaemia and bleeding because of low blood counts associated with chemotherapy.

CNS prophylaxis - people with Aids-related lymphoma have a high risk of their lymphoma spreading to the central nervous system (CNS). CNS prophylaxis is used to try to prevent cancer cells from entering the tissue covering the brain and spinal cord. CNS prophylaxis may involve giving intrathecal chemotherapy (chemotherapy drugs are injected into the cerebrospinal fluid).
(Canadian Cancer Society).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may

also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial
The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials
In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over
After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Medical Disclaimer
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