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Challenges Associated with Living with Haematological Malignancies in Sub-Saharan Africa

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Summary

The incidence of haematological malignancies is growing in sub–Saharan Africa. It currently account for about 10% of all cancers diagnosed in region. The management of these malignancies in the region is not as optimized as in most developed economies. There are several challenges associated with the effective management of these malignancies in the region; population-based cancer registries in the region is underdeveloped, suboptimal research on these malignancies, challenges with early diagnosis and appropriate treatment, suboptimal professional human and infrastructural endowment. Patients with these malignancies face several challenges, lack of optimum and safe blood transfusion support, huge cost of chemotherapeutic remedies including radiotherapy and iron chelation agents and lack of laboratory investigation for monitoring response to treatment. Success and management of haematological malignancies in Sub-Saharan Africa, need the collaboration of the entire cancer community, medical experts, teamwork, and advocacy.

Keywords: Challenges, Haematological Malignancies, Sub-Saharan Africa

Introduction

In Sub-Saharan Africa, haematological malignancies account for about 10% of all cancer deaths, making them the leading cause of mortality globally. People suffering from haematological malignancy are especially vulnerable to viral, bacterial, and parasitic infections such as HIV, hepatitis, tuberculosis, and malaria, which can increase the risk of disabilities and organ failure. Haematological cancers, such as leukaemia, lymphoma, and myeloma, significantly suppress the immune system, allowing microorganisms to infiltrate the body. However, some medical strategies can be adopted to tackle the menace of haematological malignancies in African countries and to improve the quality of patients' outcomes. Before these, the three most important steps in understanding haematological malignancies are mechanisms, prognosis, and diagnosis. Therefore, this review is aimed at discussing the cost of treatments, stigmatization, misdiagnosis, and late diagnosis associated with living with haematological malignancies in sub-Saharan Africa. The study will also investigate how Sub-Saharan African countries could adopt the global agenda for the management, success, and outcomes of patients with haematological malignancies to gain global recognition. Thus, success and management of haematological malignancies in Sub-Saharan Africa need the collaboration of the entire cancer community, the expertise of medical experts, teamwork, and advocacy.

Cancer is the leading cause of mortality and disability in developing nations, which could be due to an underfunded health system. The very recent estimate made regarding the global cancer burden in 2008, indicates that there are 12.7 million incidences of cancer cases worldwide, with 7.6 million deaths (Ferlay *et al*., 2010). Despite this alarming rate, there is the possibility of underestimation as many of the cases of cancer go unreported especially in sub-Saharan Africa due to many reasons like poor education, wrong conception about the causes of cancer and poverty, in addition to poor health systems and governance. (Story, 2012) Approximately, 6.5%

of cancer cases worldwide in 2012, have been estimated to comprise of haematologic cancer (Ferlay *et al*., 2013).

Globally, haematological cancer is the second cause of death and the fifth most frequently occurring type of cancer (Ferlay *et al*., 2015). In 2016, 8.7% of cancer incidence were diagnosed and 9.9% of cancer fatalities were caused by non-Hodgkin lymphoma (NHL), leukaemia, Hodgkin lymphoma (HL), and multiple myeloma (Bray *et al*., 2018). However, regardless of the growing prevalence, sub-Saharan Africa lacks the necessary diagnostic, therapeutic, and palliative systems. Meanwhile, even with its low resources, Sub-Saharan Africa can effectively treat and effectively manage haematologic malignancies despite several challenges (Umar *et al*., 2012).

Despite this growing burden, cancer continues to be a relatively low public health priority in Africa, largely because of limited resources and other pressing public health problems, including communicable diseases such as AIDS/ HIV infection, malaria, and tuberculosis (Parkin *et al.,* 2014). However, this could also be a result, in part, of a general lack of awareness among policy makers, the general public, and international private or public health agencies concerning the magnitude of the current and future cancer burden and its economic impact (Jemal *et al*., 2012). Other conspicuous challenges include (Faguet, 2015) lacking or inadequate infrastructure; (Rebemtulla, 2010) inadequate personnel, including Medical Laboratory Scientist, Pathologists and other medical personnel (Illiffe, 1998) insufficient opportunities for professional education or training and "brain drain" (Davies *et al*.,1962). To manage this growing burden, these factors must be addressed. The expenses that go with desired interventions often extend far beyond the health budgets of countries in the region. Therefore, a complex web of poverty, ignorance, and inadequate diagnostic and treatment facilities has made cancer outcomes worse in SSA than in other regions of the world. This explains the lack of impact at the population level, as shown by the continued rise in incidence and high mortality rates.

Haematological Malignancies

Based on the description of the World Health Organisation, haematopoietic malignancies are classified into myeloid and lymphoid malignancies. While myeloid malignancies include acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), polycythaemia Vera (PV), essential thrombocythemia (ET), myelofibrosis (MF), myelodysplastic syndromes (MDS), and myelodysplastic syndrome/myeloproliferative neoplasms (MDS/MPNss), the lymphoid malignancies include acute lymphoblastic leukaemia (ALL), mature B-cell, T-cell, or NK-cell including chronic lymphocytic leukaemia (CLL), plasma cell neoplasms, and polycythaemia Vera (PV) (Swerdlow *et al*., 2016).

In Nigeria, haematological malignancies account for about 17.4%–18.5% of all cancer cases and are the main cause of morbidity and mortality (Nwannadi *et al*., 2010). Leukaemias are more prevalent than lymphomas, with CML being the most prevalent type of chronic leukaemia (70.3%), while acute leukaemia are more prevalent than lymphomas (29.7%) (Nwannadi *et al*., 2010). Over 60 known disease subtypes exist, and each has a unique clinical presentation, therapeutic needs, and prognosis (James *et al*., 2009). Thomas Hodgkin first identified the first haematological cancer in 1832. He described a specific kind of lymphoma, which was later given the term Hodgkin's disease in his honour, more than 30 years after his death (Hodgkin,1932). Soon after, additional haematologic cancers including leukaemia and multiple myeloma had their published descriptions. Since then, efforts have been made to classify the numerous subtypes of these cancers and provide detailed descriptions. Using immunophenotyping, cytogenetics, and molecular techniques, a relatively large variety of genetically varied disorders are discovered (Lichtman, 2008). The WHO classification used the principles of the International Lymphoma Study Group's Revised European American Lymphoma (REAL) classification, including morphological, immunophenotype, genetic, and clinical factors to designate various kinds (Harris *et al*., 1999). Due to the high costs of their diagnosis and typically lengthy management, these diseases place a financial strain on the sufferers, their loved ones, and society as a whole.

Diagnosis

The following investigations play a key role in the diagnosis of haematological malignancies:

a) Full blood count
b) Peripheral blood film
c) Bone marrow aspirate
d) Bone marrow biopsy (Trephine).
e) Immunophenotyping (lymphoma and myeloma).
f) Cytochemistry.
g) Cells marker [Janus kinase -2 (Jak -2) diagnostic of MPD]
h) Biopsy of the lymph node in patients presenting with lymphadenopathy.
i) Cytogenetics (AML and CML). BCR-ABL gene is a diagnostic of CML.
j) Fluorescent in situ hybridization (FISH) (Shehu et al, 2021).

Malignant lymphomas are no longer diagnosed on an H&E-stained tissue section with a small selection of immunohistochemical assays thrown in for good measure (Ugwu and Nwannadi, 2020).

Management and Socioeconomic Challenges of Haematologic Cancers

Scarce Resources

In addition to the growing burden, there are few resources available in sub-Saharan Africa to diagnose, treat, and palliate haematological malignancies. Furthermore, about 63% of the people are living in rural areas, as reported in 2010, but these services are more available in mega population centres in most economic-resources nations (Hardin and Higgison, 2005).

Treatment

Since therapy is frequently not covered by health insurance, cost is a serious barrier to improving outcomes. Families are left with no choice except to stop receiving treatment. Diagnosis can be difficult due to limitations in radiological and pathological knowledge as well as insufficient diagnostic facilities. Most treatment facilities in sub-Saharan Africa employ unregulated generic medications. This is made worse by the inconsistent availability of medications (Stefan, 2015b).

Due to insufficient drug supply, a lot of children who might have been cured of state full name followed by abbreviation when first used (BL) are unavoidably receiving less treatment than necessary. Despite the outstanding prognosis for BL in economic-resource countries, with about 90% long-term cure rate when employing intensive chemotherapy regimens, the strategies have not been maintained. Healthcare costs are increasing steadily and have already reached what would be considered alarming levels in many sub-Saharan African nations. Due to the prevalence of cancers and the development of new, expensive cancer tests and therapies, cancer medicine plays a crucial role in this phenomenon. However, limiting the explanation of health care expenses to the issue of shamelessly increased medication prices would fall short of being thorough. To provide a full picture of the growing financial burden associated with cancer care, several types of expenses must be considered (*Table 1*). Hospital care for in-patients has the highest costs in most of healthcare systems. This is especially important for patients with haematological malignancy because, some procedures like acute leukaemia induction therapy and allo- or autologous transplants sometimes need a longer duration for staying in a hospital, with subsequent increased to hospital bills. Another money-related aspect is identified when basic patient care expenditures are added to the invoicing for new tests (Goswami et al, 2019).

Table 1: Categories of Health Care Costs

Direct	Indirect	Very indirect
Hospital in -patient care (charged per service item or blanket charge)	Loss of work power (unfit for work due to medical reasons)	Psychoses due to illness wi th decreased mental health (lack of concentration, memory loss, etc)
Hospital ou t-patient care	Unemployment due to illness	Loss of productivene ss of company employing a cancer patient
Diagnostic tests (imaging, laboratory, etc)	Reduced income	
Interventions (surgery, radi ological, etc)	Family members and other careers	Family members
Drugs		Costs for health care management (global and individu al costs per patient)
Non–drug treatment (surgery and radiation-oncology)		Costs for q uality assurance of medical services (certif icates, interlaboratory comparisons, a nd round-robin tests') (Goswami *et al* ., 2019)

Contribution of Endemic Infections to the Incidence of Cancers

About 36% of various cancers in Africa are caused by infections, which doubled the global rate (Parkin, 2008). There is significant data supporting the link between viral infections and the emergence of lymphoma. African Burkitt lymphoma is caused by Epstein-Barr virus infection, which also promotes the risk of Hodgkin disease and follicular lymphoma (Vockerodt *et al*., 2015; Young *et al*., 2016). Additionally, Hepatitis B and C infections are attributed to increased risk of non-Hodgkin lymphoma (Marcucci and Mele, 2011), with individuals who also have concurrent HIV infection (Wang *et al*., 2017).

HIV

In the developed countries, HIV is associated with the increased incidence of NHL, HL, and leukaemia (Patel *et al*., 2008). Similar increased risk incidence was also reported in sub-Saharan Africa during the antiretroviral therapy (ART) era. NHL incidence decreased but has subsequently stabilized, whereas HL incidence has been stable and may have increased. sub-Saharan Africa has been found to have a similar increased risk of both NHL and HL (Patel *et al*., 2008; Mbulaiteye *et al*., 2006). With NHL being the major common cancer-related cause, cancer's relative contribution to HIV mortality has increased, accounting for 25% to 35% of fatalities (Patel *et al*., 2008).

A decreased CD4 count, and cumulative HIV viremia are risk factors for NHL (Patel *et al*., 2008). It is interesting to note that risk for HL may be elevated in a month immediately following the start of ART and with moderate

rather than severe CD4 lymphopenia (Lanoy *et al*., 2011). Regardless of having only 12% of the world's population, sub-Saharan Africa accounted for about 22.9 million (68%) out of 34.0 million persons living with HIV globally (Patel *et al*., 2008). Despite great progress in expanding access to ART, there are still several challenges (Patel *et al*., 2008). In sub-Saharan Africa, HIV-infected individuals start antiretroviral therapy (ART) with lower CD4 numbers than people in industrialized nations. Patients who delayed starting ART have higher lifespan, CD4 lymphopenia and HIV viremia, which increases their chance of developing haematologic malignancies (Guiguet *et al*., 2009). There are still significant differences between countries in terms of ART coverage, with estimates for potential patients, from 3% to 5% in Somalia and Sudan to 88% to 93% in Rwanda and Botswana compared to the United States, where ART coverage is projected to be 75%, when they have around 49% rate (Gardener *et al.*, 2011).

In resource-limited settings, ART is now recommended at CD4 counts less than 350 cells/mm3, replacing the previous criteria of less than 200 cells/mm3 (WHO, 2010). Although the new WHO instructions that prescribed ART at CD4 levels more than 500 cells/mm^3 show that there will still be a sizable "treatment gap" between poor resource and high-income nations even if they are uniformly applied (Thompson, 2010). The higher prevalence of endemic oncogenic coinfections in sub-Saharan Africa may further increase the risk of malignant haematologic diseases. Haematologic cancers may thus become the main cause of HIV morbidity and mortality globally, as the epidemic progresses to an equivalent or to the larger extent than resource-rich environments. Since the beginning of the HIV epidemic, there have been consistent rises in NHL and, to a lesser extent, HL throughout the region. In many contexts, HIV incidence among NHL and HL patients varies from 30% to 70%. (Wiggil *et al*., 2011). Clinical trials and observational cohorts in resource-rich nations have shown comparable results for HIV-related NHL and HL to individuals without HIV, however other studies have showed HIV infection to be independently linked with mortality (Berengner *et al*., 2008; Chao *et al*., 2010). There is few information available about how HIV affects NHL survival in sub-Saharan Africa. However, reports have suggested that taking ART concurrently might improve survival compared with individuals who do not have HIV (Bateganya *et al.,* 2015).

EBV (Epstein Barr Virus)

Over 50 years ago, researchers in London cultured and used electron microscopy to study samples obtained by Denis Burkitt from Ugandan children with a newly characterized jaw tumour. This work led to the identification of EBV, as the first virus to be pathogenically linked to human cancer. Since then, EBV has gained recognition for its capacity to immortalize B lymphocytes and for its links to HL, Burkitt lymphoma (BL), nasal NK-T cell lymphoma, and B-cell NHL in individuals with immunosuppression, such as HIV (Thorley-Lawson and Gross, 2004). Compared to the rich-resource countries, the dynamics of EBV acquisition are different in sub-Saharan Africa. Infection occurs through oral secretions, and seroprevalence is almost universal in sub-Saharan Africa with acquisition occurring in early childhood, while seroprevalence in industrialized nations is roughly 75% with acquisition occurring later in life and coinciding with sexual activity (Biggar *et al*., 1978; Cohen, 2000). Even though EBV has a high global prevalence, there are notable regional and global variations in the incidence of EBV-associated cancers, possibly due to host genetics, environmental factors, or viral genetic variation. In sub-Saharan Africa, EBV has a striking and geographically distinct related with BL and HL (Chang *et al.,* 2009). Over 50% of unidentified lymphomas from sub-Saharan Africa have been found to include EBV-encoded RNA, with BL, HL, and plasmablastic lymphoma showing highest connection rates (Nwakigonja *et al.,* 2010). Additionally, HIV enhances EBV-infected B-lymphocytes by suppressing cytotoxic T-cell activity against infected B cells, which potentially leads to an oncogenic synergy in people who are also co-infected (Cohen, 2003).

Malaria

More disproportionately, sub-Saharan Africa accounts for almost 90% of the world's cases of malaria (WHO, 2010). Over 50% of unregulated lymphomas from sub-Saharan Africa have been found to include EBV-encoded RNA, with the

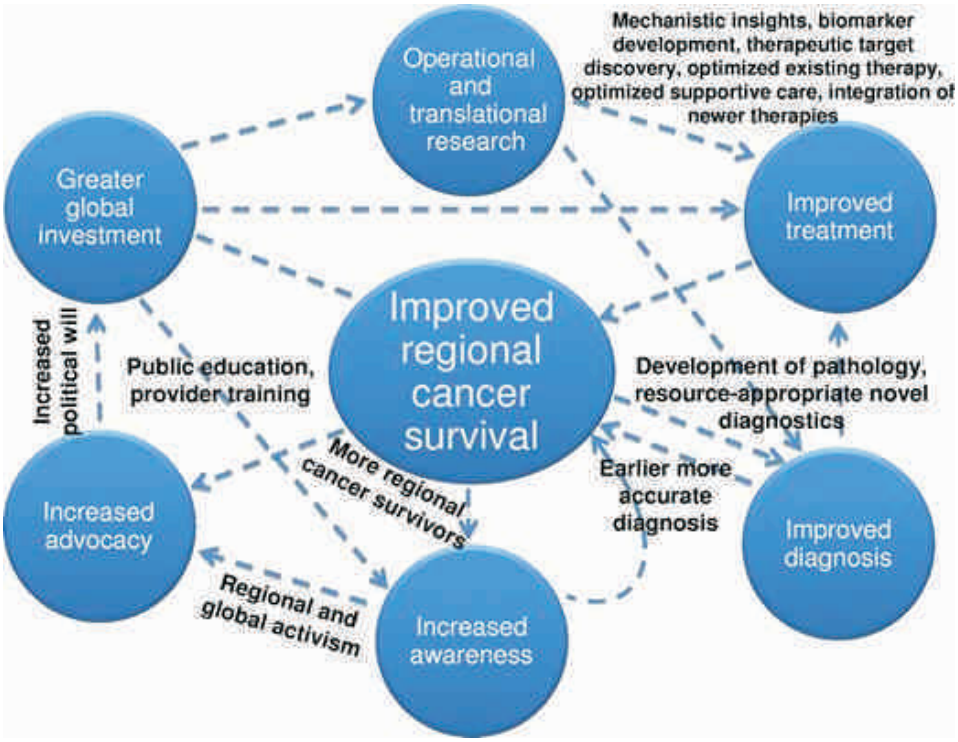
highest rates of association being seen in BL, HL, and plasmablastic lymphoma (Guech-Ongey *et al*., 2010). Since its early discovery, endemic childhood BL has been environmentally related with malaria (Geser and Brubaker, 1985). Additionally, Tanzanian measures to combat malaria have reduced the frequency of BL (Geser *et al*., 1989). Children with BL have been found to have increased levels of non-protective whole schizont antibodies in Malawi and Uganda (Carpenter *et al*., 2008), while protective antibodies against *Plasmodium falciparum* serine repeat antigen have been linked to a decreased risk of BL in Ghana (Guech-Ongey *et al.,* 2008). Although a definitive etiologic connection has not been identified, P. falciparum induces polyclonal expansion of B cells, impairs T-cell immune responses specific for EBV (Lam *et al*., 1991), which may preferentially stimulate EBV replication and expansion of EBV-positive B-cell expression by virtue of its cysteine-rich interdomain region 1 (Chene *et al.*, 2007). Pesticides, bed nets, sociocultural practices, and other environmental factors, on the other hand, have an impact on malaria transmission, and may modify the risk of BL by altering some cofactors, including intestinal parasites or immunological responses to EBV (Ongwang *et al*., 2008).

Palliation

In the industrialized world, palliation is a key duty of oncologists, yet despite receiving the best possible care, cancer patients frequently succumb to death. In sub-Saharan Africa, palliative care is not widely available. They are limited by the availability of opioids as well as by regulatory restrictions that prevent the administration of opioids even when they are available. Even though morphine has been a WHO essential medication since 1977 (Selman *et al*., 2011).

Improvement for the survival of patients with haematological malignancies in sub-Saharan Africa is a heavy task. The figure below highlighted a conceptual framework model that provides a collateral benefit to minimise morbidity and mortality from non-haematologic malignancies. Local growth is essential for effective cancer programs. There will be a reasonable discussion about what is appropriate, doable, and attainable across the region (Umar *et al*., 2012).

Figure : A Conceptual Framework for Enhancing the Survival of Patient with Haematological Malignancies in Sub-Saharan Africa



Source: (Satish *et al*., 2012).

Some Measures to be considered include:

1. Create traditional and cutting-edge diagnostics tailored to the environment.

It is imperative to develop histopathology, enhance tissue collection and processing, and apply fundamental immunohistochemistry. However, it is difficult to successful graft pathology systems from industrialized nations into diverse environments without changes. Conventional practices may be augmented, and in some cases, replaced, by tissue microarrays, digital microscopy techniques, and diagnostic algorithms that are appropriate for the local environment, as facilitated by the INCTR and sub-Saharan Africa Lymphoma Consortium (Harris *et al*., 1999). Furthermore, distinctive genetic abnormalities and subsequent molecular events are increasingly used to identify malignancies from other diseases. Due to poor laboratory infrastructure, genotypic and nucleic acid amplification assays are currently not extensively implementable in the region. However, PCR techniques using dried blood spots have been created especially for use in areas with limited resources to enable HIV diagnosis in infancy, RNA sequencing for HIV monitoring, and HIV resistance detection (Gardener *et al.,* 2011). In a similar vein, a fully automated, cartridge-based molecular diagnostic device has been created to identify tuberculosis and identify drug resistance, enabling earlier initiation of the treatment (Chao *et al*., 2011). These methods are intended for application in environments with decentralised specimen collecting, slow specimen transport, and constrained technical resources in the laboratory. Even in lower-level health institutions, they have been successfully deployed, and their price is affordable for sub-Saharan Africa (Chao *et al.,* 2011). It is feasible that such technology may one day make cancer diagnosis, treatment, and response assessment possible in a situation lacking conventional pathology facilities or advanced diagnostic imaging.

2. Reduce the Cost of Cancer Medications and Consider Incorporating Innovative Therapies.

The molecular era has accelerated the transition from cytotoxic therapy to "targeted" medicines focused on immunophenotypes, mutations, and gene products. Monoclonal antibodies, antibody-drug conjugates, small molecule tyrosine kinase inhibitors, immunomodulatory drugs, proteasome inhibitors, and histone deacetylase inhibitors are a few non-cytotoxic medications that have recently been added to the arsenal for treating haematologic malignancies. Even in environments with huge number of resources, many of these agents' ideal applications are still being researched (Hardin and Haggison, 2005). Moreover, their current price makes them unaffordable for use in sub-Saharan Africa. However, putting financial concerns aside, they are the best treatments for the area. Many have more tolerable toxicities than conventional cytotoxic drugs, such as less myelosuppression and an increased risk of infectious diseases when taken orally, eliminating the need for infusion. The "newest" WHO critical cancer medication is 20 years old, as previously mentioned, and we believe that depriving people in sub-Saharan Africa of newer medicines is wrong, resist the fundamental tenet of the WHO and UN that "health is a human right" for a few more decades (WHO, 2010). In environments where genetic variations, common comorbid illnesses, nutritional status, interactions with co-administered medications, adherence, and other factors may result in efficacy, safety, and cost-effectiveness profiles different from previously studied populations, developing platforms to study integration of newer agents is important. The Clinton Health Access Initiative has been a driving force behind successful ART in sub-Saharan Africa by negotiating deals with manufacturers to deliver HIV medications at low cost (typically 10% of the US retail price) (Berenguer *et al.,* 2008). Similar tiered pricing structures may be possible for particular cancer therapies that have been shown to be safe and efficient in the area, particularly if they are linked to higher rates of long-term medications. Rituximab and imatinib's patents are about to expire, and generic versions and biosimilars are already being developed and tested in clinical settings (Berenguer *et al.,* 2008).

3. Evaluate the Cost-Effectiveness of Cancer Control Strategies and Increase Global Financing for Cancer Research

While South Africa alone accounted for 51% of the $581 million (US) in regional cancer expenditures, sub-Saharan Africa accounted for 5.4% of new cancer cases globally in 2009 but with only 0.2% of

worldwide cancer spending. By contrast, $2.8 billion (US) was spent on HIV in sub-Saharan Africa in 2009 (Berenguer *et al.,* 2008). Even in industrialized nations, it has been difficult for governments and health systems to sustainably finance contemporary cancer care. Resources are limited in sub-Saharan Africa, thus a logical discussion on how to use and increase available resources is required. This discussion will involve input from patients, doctors, policymakers, economists, and ethicists. Cancer treatment will be predictably more expensive than treating chronic conditions like HIV. For instance, the price of 6 cycles of cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin) and prednisolone (CHOP) is about $1500 (US). Cost-effectiveness may, however, compare favourably with other recognized therapies, especially, if the treatment is taken by decades of event-free survival. In settings with low resources, the current yearly cost of ART is around $200 (US) for first-line treatment and between $500 and $600 (US) for second-line treatment (Hardin and Haggison, 2005). Future initiatives will include formal cost-effectiveness analyses of cancer, control strategies as well as the development of moral regional guidelines for affordable cancer treatment.

4. Increase Human Resources for Cancer Research

Even though the non-oncologists can provide cancer treatment in a safe and efficient manner (McGrath and Joske, 2002), it is urgent to address the essential lack of healthcare professionals. It is crucial to make investments in a clinical, pharmacy, and laboratory workforce that has experience in managing cancer patients. International organizations including the American Society of Haematology, ASCO, INCTR, NCI and African organizations (West African College of Medicine) have made training initiatives a primary priority. Presently, the NCI is now funding 3-year-long pathology training seminars in Kenya to increase regional capability. Programs like the Medical Education Partnership Initiative offer specific financing sources to assist training initiatives. However, it will take decades of persistent effort to create a committed oncology staff and reverse decades of "brain drain," so creating intermediate plans is crucial. Works shifting and other creative human resource management techniques have frequently been used to overcome physician shortages in the fight against infectious illnesses (Shehu *et al*., 2011). Further research should be done to determine whether video conferencing and telepathology are appropriate for cancer awareness and treatment in the area.

Conclusion

Due to the immense grossly increasing burden, some people might feel pessimistic about the chances of regulatory haematologic malignancies in Sub-Saharan Africa. Even though there are still many challenges to overcome and a lot of work to be done, the global response to HIV offers an essential lesson. As a consequence of persistent international campaigning, cooperation, and investment, where there was once existential concern about the future of entire nations, there is rising optimism and open demands to stop the epidemic to our lives. In the years to come, sub-Saharan Africa will have a comparable chance to significantly impact cancer control. By overcoming this obstacle, the continent will reduce the suffering of millions of people affected by cancer and turn many patients into long-term survivors. It is also expected to uphold the mutualistic ideal embodied by the first BL cooperation in Uganda, and perhaps learn something that will help with the creation of new, universally applicable treatments. Thus, success and management of haematological malignancies in Sub-Saharan Africa, need the collaboration of the entire cancer community, medical expert, teamwork, and advocacy within sub-Saharan Africa which is the key to achieve this success.

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