Similarities in Asymptomatic HIV Infection and Cancer: *A Common “Driver” Hypothesis*

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Abstract Cancer and Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) are associated with chronic oxidative stress, inflammation and immune activation either as a consequence or a cause. Despite well documented characteristic similarities in the two diseases, this has not been exploited for better understanding of carcinogenesis. The purpose of this descriptive study was to review existing studies for knowledge, research gaps in the role of oxidative stress, inflammation, immune activation in cancer and asymptomatic HIV infection; identify similarities, differences to stimulate new research ideas which can accelerate future therapeutic target discoveries. PubMed, ScienceDirect and Google scholar databases were searched using the keywords: oxidative stress, inflammation, immune activation, cancer and asymptomatic HIV infection. Little research has been done on immune evasion, tolerance and oxidative stress-induced inflammation and immune activation as therapeutic targets in both diseases. Senescence and the role of respiratory burst in HIV infection have not been exhaustively studied. Out of a total of 15,788,387 hits, 15, 284,572 hits related to similarities with only 503, 815 relating to the differences between the two diseases. Consequently and after pearling, 89 articles that were directly relevant to the study were selected. After critical appraisal, the identified studies were analyzed, results compared and presented in form of summary tables. Results indicated that chronic oxidative stress, inflammation and immune activation were common drivers of progression in the two diseases. Therefore, better understanding of these drivers might provide new mechanistic insights in carcinogenesis and provide future novel therapeutic targets. This will support the United Nations sustainable development goal (SDG) number 3 on ensuring health lives and promoting well-being for all at all ages.

Keywords Oxidative Stress, Inflammation, Immune Activation, Cancer, Asymptomatic HIV Infection

1. Introduction

The emergence of non-communicable diseases (NCDs) such as cancers has added to HIV/AIDS burden especially in resource-limited settings in the sub-Saharan Africa [1, 2]. Annually, approximately 40,000 Kenyans are diagnosed with cancer, of which, about 27,000 dies within 1-2 years of diagnosis [3]. Likewise, about 80,000 annual HIV/AIDS-related deaths and 100,000 new HIV infections occurred in Kenya in 2012 [4]. This makes the two diseases the leading causes of mortality in Kenya [5]. Importantly, with the expected prolonged life of people living with HIV/AIDS due to universal access to antiretroviral therapy, HIV-related malignancies are expected to increase 200 fold, aggravating an already dire situation [6].

Cancer and HIV/AIDS are associated with chronic oxidative stress, inflammation and immune activation, though degree varies, hence similarities and differences in their effects in the two diseases [7, 8]. For that reason, understanding, drivers of these similarities and differences, their impact in the two diseases could be exploited for better understanding of carcinogenesis, cancer progression and maintenance. Regrettably, there is no data currently on studies relating the two diseases, despite existing of extensive, data on the independent diseases.

In addition, to stimulating more research interest in carcinogenesis, providing future novel therapeutic targets, providing preventive, screening, early diagnosis strategies and policies, such studies will have a direct impact on cancer management.

Current Knowledge in Carcinogenesis

The influence of free radicals, proto-oncogenes, oncogenes on initiation, promotion and evolution towards malignancy has been known from as early as 1990 [9]. Significantly, oxidative stress has been recognized as a potent initiator of the consistent NF- κ B activation strongly associated with chemical tumorigenesis, tobacco, alcohol, high-fat diet, environmental pollutants, cancer-inducing viruses (HIV, HPV, Hepatitis B,C), bacteria (*H. pylori*), ultraviolet light, ionization radiation and obesity-associated

cancers [10,11]. Furthermore, oxidative stress has been recognized as the “master key” through which tumour microenvironment interacts with almost all cancer hallmarks [12].

In cancers, persistent but moderate viral, bacterial or other carcinogens-induced oxidative stress, inflammation and immune activation leads to formation of lesions eliciting a vicious cycle of the same and persistent nuclear factor of Kappa B (NF- κ B) signaling [13,14]. Though persistent, the NF- κ B signaling is not strong enough to lead to apoptotic signaling, this together with cellular adaptations to reactive oxygen species (ROS), such as change to replicative immortality signaling by antioxidant defenses enables resistance to cell death as a defense mechanism [15].

ROS and oxidative stress's capacity to induce metabolic reprogramming [14], stimulate proliferative signaling [16, 17], activate angiogenic signaling [18], influence cellular senescence [19] as well as induction of deoxy nucleic acid (DNA) damage [17] has been reported previously. Furthermore, majority of cancers, especially solid tumours, myeloproliferative disorders commence in a setting of oxidative stress and inflammation [20, 21]. Importantly, chronic inflammation, though commonly caused by infections, can also be produced by exposure to carcinogens such as irradiation and environmental chemicals [22, 23].

In cancers, oxidative stress and glycolytic influx is thought to lead to metabolic reprogramming [24], while increased respiratory burst in asymptomatic HIV infection has been reported [25,26,27,28]. In addition, chronic oxidative stress impacts on the immune status of the host by activating the innate and adaptive cells, thereby compromising immunosurveillance [29].

Consequently, the host's immunity plays a critical role in determining cancer initiation and its progression [30]. Interestingly, immunosuppression has been recognized as the biggest risk factor for solid tumours such as non-Hodgkin lymphoma [31]. Essentially, cancer is associated with increased immune activation of both innate and adaptive immune systems, characterized by expression of tumour antigens, cytokines production (Interleukin 8 [IL-8], transforming growth factor beta [TGF- β], tumour necrosis factor alpha [TNF- α], IL-1 and IL-6), induction of immunosuppressive FOXP3+ T-regulatory cells (T-regs), down regulation of major histocompatibility complex I (MHC I) molecules on cytotoxic T-cells (CD8+ T-cells) [32,33], dysfunctional CD8+ T-Cells, all believed to be driven by oxidative stress and or inflammation [34, 35,36]. In addition, T-regs have been shown to be essential for K-Ras-mediated lung tumorigenesis [37]. A “bystander effect” produced by ROS and nitrogen oxide (NO) radicals from activated macrophages are thought to contribute to genomic instability and leukomogenesis [39].

Cancer development and progression is characterized by the following seven hall marks [33, 34];

1. *sustained proliferative signaling*
2. *evading growth suppression*
3. *activating tumour invasion and metastasis*

4. *enabling replicative immortality*
5. *inducing angiogenesis*
6. *resisting cell death*
7. *immune evasion and tolerance*

Current Knowledge in Asymptomatic HIV Infection

Depending on the severity of symptoms, world health organization (WHO) classifies HIV infection into four clinical stages; clinical stage 1 or asymptomatic stage, which has no symptoms or characterized by general lymphadenopathy, clinical stage 2 with mild symptoms, clinical stage 3 with advanced symptoms and clinical stage 4 or the acute AIDS phase with severe symptoms such as the HIV wasting syndrome among others [39]. The hallmark of HIV infection is the massive depletion of CD4+ T-helper cells and the subsequent inability to fight opportunistic infections [40]. This occurs during the early phases of HIV infection, more specifically, stage II of HIV infection and has been associated with increased free radicals (ROS) generation [41, 42, 43, 44]. Similarly, some viral proteins (such as Vpr) are capable of binding to mitochondria of infected CD4+ T-cells, directly inducing apoptosis [45]. Hence, asymptomatic HIV infection is characterized by chronic oxidative stress, inflammation and immune activation, which are associated with the massive depletion of CD4 T-Cells [13, 46].

Oxidative stress has been defined as the cytopathological consequence of an imbalance between free radical production and the antioxidant status of the cell by Franco & Panayiotadis, (2009) [47]. This is believed to contribute considerably to the death of CD4+ T-lymphocytes in HIV infection, thereby aiding progression to AIDS [48, 49, 50]. Further, the sensitivity of immune cells to oxidative stress due to high polyunsaturated acyl lipids in their plasma membrane makes them vulnerable to peroxidation. As a result, their biomolecules such as DNA, carbohydrates, protein and uric acid are prone to oxidative damage by ROS [51, 52]. Specifically, hydrogen peroxide (H₂O₂) and other oxidants generated by activated neutrophils, macrophages in HIV infection during respiratory burst (due to increased energy demands), adenosine triphosphate (ATP) production, during inflammation [54], promotes tissue injury and inflammation [55, 56]. As a result, respiratory burst, which has been reported in asymptomatic HIV infection, is believed to contribute to the overall oxidative stress and the associated massive death of CD4+ T-cells in early HIV infection [27, 56].

Increased ROS and oxidative stress in HIV infection, leads to persistent NF- κ B signaling, which ultimately causes apoptosis (programmed cell death) of CD4 T-lymphocytes. Likewise, translocation of microbial products, such as lipopolysaccharides (LPS) across the gastrointestinal tract (GIT) mucosal lining during early HIV infection adds to the persistent immune activation and inflammation [45, 57, 58]. Consequently, the “leaky gut” phenomenon has been identified as an essential source of the characteristic persistent immune stimulation in HIV infection [59, 60].

Accordingly, this results in oxidative stress, dysfunctional immune system, pro-inflammatory cytokine production, inflammation-associated complications and uncontrolled viral replication in activated CD4+ T-cells [56, 61]. For that reason, increased immune activation, inflammation and oxidative stress have been linked to death of immune cells, rapid disease progression and a higher risk of death [59, 62, 63, 64].

In addition, early HIV infection is characterized by immune evasion and tolerance through down regulation of MHC I molecules on CD8 T-lymphocytes. As a result, CD8 T-cells becomes dysfunctional, cannot recognize or destroy virally-infected cells, thereby enabling immune evasion and tolerance common in HIV/AIDS. Recently, Nolan *et al.* (2016) [65] reported that T-cell activation levels expressed as CD38 on CD8+ T-cells, predicted a poor prognosis for the HIV infected patients, which has been confirmed by other investigators [59, 66, 67]. The persistent systemic immune activation in HIV infection results in increased pro-inflammatory cytokines generation such as TNF- α , IL-1 and 6, which have been implicated in the activation of extrinsic pathway of apoptosis [57, 68]. Subsequently, the generated pro-inflammatory cytokines drive several processes underlying the inflammatory response, cell apoptosis, activation and differentiation [69, 70]. As a result, markers of inflammation, immune activation have been recognized as stronger predictors of HIV progression to AIDS than CD4 count and viral load [71].

Objectives

To investigate the hypothesis that oxidative stress, inflammation and immune activation drives the characteristic similarities in pathophysiology of cancer, early HIV infection, the author reviewed existing literature to identify critical knowledge gaps, unmet research needs specifically on interrelations between oxidative stress, inflammation, immune activation in relation to the two diseases.

The objectives of this descriptive review were to:

1. Review existing literature for similarities, differences in pathophysiology of cancer and asymptomatic HIV infection,
2. Identify knowledge, unmet research gaps in order to stimulate further research interest in the field.
3. Exploit the identified knowledge, research gaps to generate new hypothesis, new mechanistic insights in carcinogenesis, tumour maintenance, progression in order to accelerate discovery of new therapeutic targets and preventive strategies.

The author was trying to answer the following review questions whose answers hold the key to understanding carcinogenesis, cancer maintenance and its progression:

1. At what point does apoptotic and or NF- κ B signaling common in cancer and HIV shift to sustained proliferative signaling/replicative immortality in cancer and why?

2. What drives the shift in apoptotic signaling; i.e. from cell death of CD4-T-lymphocytes in asymptomatic HIV infection to resistance to cell death (apoptosis)/proliferative signaling/replicative immortality in cancer?
3. What causes metabolic reprogramming in cancer and only an increased respiratory burst in HIV?
4. What causes cellular senescence in HIV/AIDS and why is it absent in cancer?
5. What causes clonal selection in cancers and why is it absent in HIV?
6. What is the impact of oxidative stress, inflammation and immune activation in cancer and asymptomatic HIV infection?
7. What is the role of immune system in progression of cancer and HIV/AIDS?

2. Materials and Methods

This was a descriptive review of the existing literature on cancer, asymptomatic HIV infection, their similarities and differences in pathophysiology. This study was conducted at Kirinyaga University from 5th March 2016 to 27th February 2017. The inclusion criteria was only full text articles in English, publications on processes, mechanisms in early HIV infection, oxidative stress, antioxidants, metabolic reprogramming, respiratory burst, hypoxia, apoptosis, inflammation, immune activation, major histocompatibility molecules, immune evasion, tolerance, senescence, mutations, clonal selection, therapeutic targets in cancer and asymptomatic HIV infection. The exclusion criteria was all publication not in English language, not directly associated with the search words; asymptomatic HIV infection, cancer, oxidative stress, inflammation, immune activation, publications involving all the other diseases apart from cancer and asymptomatic HIV infection.

The keywords were developed by breaking down the review questions. From the objectives and review questions, a search strategy using different combinations of the key search words in relation to either asymptomatic HIV infection or cancer was devised and applied. The following databases; PubMed, Google scholar and ScienceDirect were searched and downloaded at Kirinyaga University from 6th of April, 2016 to 30th November, 2016, using the previously identified keywords. A total of 15,788,387 hits for both similarities and differences between the two diseases were obtained. After pearling, critical appraisal of the studies to assess the relevance to the current study, quality, what was analyzed, results obtained of the downloaded articles, 89 articles were selected. The articles were reviewed and the relevant background information, current knowledge in important similarities, differences between the two diseases, research gaps in the field identified, highlighted, compared and documented. The results of the relevant articles were compared, appraised, analyzed, summarized and presented in the form of summary tables.

Table 1. Existing studies related to the identified similarities in cancer and asymptomatic HIV infection

Databases/Cancer	↑Oxidative stress	↓Antioxidant	↑Inflammation	↑Hypoxia	↑Immune activation	↓MHC	Mutations	Immune evasion & tolerance	Oxidative stress, inflammation and immune activation as therapeutic targets
PubMed	*224	6,595	12,925	68,177	4424	*697	220,071	*188	*5
Google Scholar	2,080,000	955,000	3,140,000	1,260,000	2,910,000	58,300	3,270,000	38,100	139,100
ScienceDirect	85,169	75,531	181,344	52,755	126,315	8,065	271,724	1,993	*589
Total	2,165,393	1,037,126	3,334,269	1,380,932	3,040,739	67,062	3,761,795	40,281	139,694

Table 2. Existing studies related to important similarities between asymptomatic HIV infection and cancer

Databases/Asymptomatic HIV infection	↑Oxidative stress	↓Antioxidant	↑Inflammation	↑Hypoxia	↑Immune activation	↓MHC	Mutations	Immune evasion & tolerance	Oxidative stress, inflammation and Immune activation as therapeutic targets
PubMed	*2	*2	*35	*0	*53	*1	*162	*1	*0
Google Scholar	19,600	13,300	81,400	18,600	79,800	6360	49,900	*5,630	10,900
Science Direct	1,822	1334	9605	2012	7647	*751	7,333	*280	*751
Total	21,424	14,636	91,040	20,612	87,500	7112	57,395	5911	11,651

Table 3. Existing studies relating to important differences between cancer and asymptomatic HIV infection

Studies common differences/ Cancer	Metabolic reprogramming	Apoptosis resistance	Clonal selection
PubMed	*1053	24127	*1514
Google scholar	57400	19400	236100
Science Direct	*5334	77319	20691
Total	63,787	120,846	258,305

Table 4. Existing studies relating to important differences between asymptomatic HIV infection and cancer

Studies common differences/ Asymptomatic HIV Infection	↑Apoptosis	Respiratory burst	Senescence
PubMed	47	*4	*38
Google scholar	32,300	17800	5320
Science Direct	3927	*947	*494
Total	36,274	18,751	5852

3. Results

Table 1 summarizes existing studies on identified important similarities in cancer and asymptomatic HIV infection. Although, cancer, oxidative stress, mutations, increased inflammation, hypoxia, immune activation are widely studied, however, oxidative stress, inflammation, immune activation as therapeutic target, immune evasion and tolerance field is not as widely studied presenting a fertile ground for future research. * indicates not adequately published area.

Table 2 summarizes existing studies on identified important similarities in asymptomatic HIV infection and Cancer. Asymptomatic HIV infection, oxidative stress, antioxidants, inflammation, hypoxia, immune activation, mutations area is widely studied. However, asymptomatic HIV infection in relation to, MHC, immune evasion, tolerance, oxidative stress, inflammation and immune activation as therapeutic targets is not as widely studied providing a fertile ground for future research. * indicates not adequately published area.

Table 3 summarizes existing studies related to cancer and asymptomatic HIV infection as downloaded using the different databases. The studies relates to cancer, metabolic reprogramming, apoptosis, clonal selection, which are important differences in cancer and asymptomatic HIV infection, processes and mechanisms. Cancer, metabolic reprogramming, apoptosis resistance (resistance to cell death) and clonal selection field is widely studied. * Indicates not adequately published area.

Table 4 summarizes existing studies related to asymptomatic HIV infection and cancer as downloaded using the different databases. Apoptosis in asymptomatic HIV infection is well studied; however, respiratory burst and senescence are exhaustively studied providing and ideal area for future studies.* indicates areas not adequately published.

4. Discussion

Based on the search words; oxidative stress, cancer, asymptomatic HIV infection, chronic inflammation and immune activation, 15,284,572 from the total hits related to similarities between asymptomatic HIV infection and cancer were obtained. Only 503, 815 hits relating to the differences between the two diseases were obtained and after critical appraisal to assess their quality, methods, what was analyzed in the studies, results and relevance to the survey, 89 articles were selected. The results of the selected studies were compared and presented in form of summary tables as shown above.

Although oxidative stress, mutations, increased inflammation, hypoxia, immune activation in relation to cancer were widely studied according to the findings of this study, however, studies on oxidative stress, inflammation, immune activation, immune evasion and tolerance as therapeutic target were few, making these areas ideal targets for future research. Specifically, future research should focus on targeting signaling pathways involved in oxidative stress-induced inflammation, immune activation, how tumour cells evades the host's immune system or induces tolerance. Precisely, the role of oxidative stress and or ROS if at all, in rendering CD8-T lymphocytes dysfunctional, down regulation of MHC I on their surfaces as well as a possible role in induction of the immunosuppressive T-reg's present in both cancer and asymptomatic HIV infection should be delineated. This might provide novel, ideal future therapeutic targets and preventive strategies.

Notably, apoptosis in asymptomatic HIV infection is well studied; however, respiratory burst and senescence are not exhaustively investigated. This provides a perfect area in which future studies can focus their attention. Precisely, studies on the role of oxidative stress and or ROS in increased respiratory burst in asymptomatic HIV infection

are required. Likewise, their role in the massive CD4 T-cells death, increased HIV replication, expression, dissemination and induction of “escape mutations”, HIV variants among other survival adaptations the virus acquires during this phase should be delineated. Mburu *et al.* (2013) [28], albeit in a pilot study, were able to show increased respiratory burst in asymptomatic HIV infection and its contribution to the death of CD4 T-lymphocytes during this stage of this infection.

According to previous studies, increased and persistent ROS, oxidative stress-induced inflammation and immune activation are thought to cause sustained NF- κ B and Ras signaling. Furthermore, increased ROS attack, oxidative stress, increased energy demands, competition for inadequate nutrients, oxygen by the rapidly dividing cells (thought to cause metabolic reprogramming and glycolytic influx), hypoxia, DNA damage, defects in cell cycle check points and dysfunctional telomere are believed to provide the selective pressure, which causes the cells to switch from apoptosis to resistance to cell death and undergo clonal selection as a survival adaptation for the harsh environment [71,72]. Subsequently, cells acquiring resistance to apoptosis are frequently more difficult to treat as they are also resistant to chemotherapies which primarily function by inducing apoptosis. For that reason, future therapeutic strategies should be designed with this resistance to cell death knowledge and ways of reversing, eliminating it or promoting apoptosis in mind [73].

The absence of rapidly dividing cells in asymptomatic HIV infection, hence no competition for inadequate resources but presence of the persistent oxidative stress attack, inflammation and immune activation, eliminates need for the cell to adapt or switch to resistance to apoptosis or cell death. However the ROS attack, resultant oxidative damage, viral load, infection, viral proteins and persistent NF- κ B signaling are enough to activate apoptotic signaling in the CD4-T-cells to undergo apoptosis. Metabolic reprogramming in cancer is thought to be caused by the increased energy demands from the rapidly dividing cancer cells, oxidative stress, while the HIV infection and translocation of microbial products (LPS) from the gut to systemic circulation as a result of loss of integrity of gut mucosa (leaky gut) in asymptomatic HIV infection is believed to cause the increased respiratory burst [74, 75].

According to previous studies and findings of this study, senescence or activation of telomerase in carcinogenesis was probably an adaptations mechanisms by the rapidly dividing cells to compete favorably for the scarce nutrient resources and survive the persistent ROS or oxidative stress attack, which is absent in asymptomatic HIV infection [76]. Activation of telomerase activity by ROS and other carcinogens is believed to lead to senescence in cancer, but is absent in HIV infection [77]. Since the highly metabolizing, rapidly dividing cells requires new blood vessels to serve the new cells, the ensuing oxidative stress, hypoxia are important in induction of angiogenesis via induction of

hypoxia-inducible factor I (HIF-I) and vascular endothelial growth factor (VEGF) [78].

Likewise, competition for inadequate nutrients, oxygen and cellular adaptations by the rapidly dividing cells which is present in cancer but absent in asymptomatic HIV infections could explain clonal selection present in cancer but absent in HIV [79]. While viral infection, translocation of microbial products from the gut to systemic circulation as a result of loss of integrity of gut mucosa causes oxidative stress, inflammation and immune activation in asymptomatic HIV infection: ROS, intrinsic oxidative stress, chemical carcinogens, cancer causing infectious bacteria, viruses and resultant tumour associated inflammation (TAI) are the source in cancer [10]. In both cancer and HIV/AIDS, immune activation, complement system activation, impairing of the immune system, CD8 T-cells damage are common features. In addition, increased generation of several cytokines, chemokines (interferons & pro-inflammatory cytokines), growth factors, decreased antioxidant defenses, down regulation of MHC molecules and induction of the immunosuppressive T-regs are characteristic of the two diseases. Importantly, the integrity of the immune system determines the rate of progression of HIV to AIDS, prevention, recovery in cancer and is a risk factor for non-Hodgkin lymphomas [31]. Further, anti-apoptotic genes such as Bcl-2, Bcl-X are upregulated in cancer but downregulated in HIV, while pro-apoptotic genes e.g. Bax, Bak, Bim, Bad are down regulated in cancer and upregulated in HIV. Interestingly, whereas excess oxidative stress, inflammation, immune activation leads to apoptosis of CD4 T-cells, in asymptomatic HIV infection, they are believed to cause resistance to apoptosis or replicative immortality cancer [48, 76, 78].

According to current literature, several factors were implicated in the shift from apoptotic signaling to replicative immortality or resistance to apoptosis such as; chronic cytokine activation from failed resolution of tumour associated inflammation [77, 78, 79], as an adaptation to oxidative stress, decreased antioxidant defenses, competition for scarce resources nutrients, oxygen by the rapidly dividing cells, persistent attack from ROS, ensuing hypoxia, inhibition of caspases due to decreased glutathione or glucose influx, activation of telomerase by ROS, oxidative stress-induced metabolic dysregulation. This is believed to activate or cause “driver mutations” in proto-oncogenes (Ras & c-Myc), inducing mutations and inactivating tumour suppressor genes (p153 & Rb) [74, 79]. Importantly, absence of this competition for nutrients and oxygen in HIV/AIDS eliminates the need for the cellular adaptations. However, the persistent ROS, oxidative stress and inflammation still impacts on cells leading to apoptosis of the infected and affected CD4 T-lymphocytes. The increased catabolic and anabolic demands from the rapidly dividing cells which is absent in asymptomatic HIV infection, increased competition for nutrients, ROS, oxidative stress are thought to be the drivers of metabolic reprogramming characteristic

of carcinogenesis. Significantly, clonal selection arises from the competition for scarce resources from the rapidly dividing cancer cells. The drivers of oxidative stress, inflammation and immune activation in cancer are mainly the infectious agents (cancer-causing viruses & bacteria), exposure to carcinogens such as irradiation, ROS or environmental chemicals [22, 23], while the virus and translocation of microbial products from the gut mucosal to systemic circulation are the drivers in HIV infection [46]. Notably, anti-apoptotic genes are upregulated in cancer whereas pro-apoptotic genes are down regulated. The opposite is true in asymptomatic HIV infection [79]. Since cancer is multifactorial in aetiology involving many pathways, processes, a multiprocess and multitarget therapeutic approach is recommended as opposed to single enzyme and or pathway targeting [75].

Identified Knowledge, Research Gaps and Future Research Direction

Despite cancer and HIV being non-communicable disease and infectious diseases respectively, striking similarities in their pathophysiology are well recognized. These similarities include; persistent NF- κ B signaling, altered metabolism (glycolytic influx & metabolic reprogramming) in cancer versus increased respiratory burst in HIV. Similarly, HIV is caused by a virus while several virus-inducing cancers such as *Epstein Barr Virus (EBV)*, *Human papilloma virus (HPV)*, *Hepatitis B & C* and *emerging HIV associated malignancies* exists. Significantly, development of mutations such as “driver mutations” of proto-oncogenes (Ras & Myc) and tumour suppressor genes (p53 & Rb) in cancer [81], “escape mutations” in HIV [82,83], induction of immunosuppressive T-regs, immunosuppression and decreased immunosurveillance role in both (e.g. increased risk of cancer development in HIV-infected patients and organ transplant recipients) have been reported. Further, residual cancer stem cells (CSC) in cancer versus residual latent HIV infected CD4 T-cells, increased replication of the virus and its dissemination versus rapidly dividing cell in cancer, metastasis, invasion of tumour cells, decreased antioxidant defenses in both, dysfunctional CD8 T-lymphocytes by down regulation of MHC I molecules on CD8 T-cells in both diseases [30, 31], have been highlighted in previous studies. Significantly, chronic oxidative stress, inflammation and immune activation have been reported to be common in both the diseases [32, 34, 35]. Therefore, the author hypothesizes that these similarities are correspondingly initiated, driven and the “common driver” is believed to be the chronic oxidative stress, inflammation and immune activation, which characterizes the two diseases. Interestingly, oxidative stress has been recognized as the “master key” through which tumour microenvironment interacts with almost all cancer hallmarks [12].

However, in addition to the similarities, characteristic differences between the two diseases exist. These include

CD4 T-cells being the primary targets in HIV infection while several cell lineages can be targeted in cancers, clonal selection occurring only in cancers but absent in HIV infection. Significantly, apoptosis of CD4 T-lymphocytes occurs in HIV infection leading to massive death of the cells as opposed to resistance to apoptosis or cell death, sustained proliferative signaling, replicative immortality of cancer cells, leading to uncontrollable cell division and development of tumours in cancer. Senescence (aging) of T-cells as a result of thymus burn out, which is present in advanced HIV infection, is absent in cancer. Interestingly, cancerous cells do not senesce and have increased telomerase activity, attributed to ROS attack, persistent oxidative stress and which are thought to also contribute to metabolic reprogramming characteristic in cancers. Of specific importance, despite the stated similarities, HIV/AIDS is caused by a virus (HIV), while cancer has a multifactorial etiology that includes viruses, bacteria, chemical, environmental carcinogens and ionization [84, 85, 86, 87].

Understanding the common drivers or pathophysiology of these similarities and differences can be applied to understand better carcinogenesis and its progression. Evidence from previous studies analyzed confirms presence of chronic oxidative stress, inflammation and immune activation in the two diseases making the author to hypothesize they are the “common drivers” of the similarities in pathophysiology of the two diseases. However, he recommends further studies specifically focusing on the role and impact of the same in the two diseases specially focusing on carcinogenesis to support and further strengthen this hypothesis.

Future Challenges

Although, the areas of cancer and asymptomatic HIV infection are well studied independently (as show in Tables 1-4) and important similarities, differences between the two documented, currently, no studies have ever linked the similarities and differences between the two, thus missing the opportunity to exploit this knowledge for better understanding of the two diseases. Despite, previous studies clearly highlighting some common similarities shared by cancer and asymptomatic HIV infection, this important knowledge has never been applied to understand better carcinogenesis, tumour maintenance and progression, which could accelerate development of therapeutic targets and preventive strategies. The rate at which cancer is killing people especially in resource limited settings such as Kenya, does not give us any laxity to miss such a massive opportunity, these similarities and differences between the two diseases offer . Of major importance as discussed in the introduction and indicated by the results in Table 1, 2, the numerous similarities in pathophysiology shared by the two diseases suggest a common driver. This evidence emboldens the author’s believe that chronic oxidative stress,

inflammation and immune activation, which characterizes the two diseases are the “drivers” of the similarities identified. Importantly, and in support of this hypothesis, inflammation, immune activation have been recognized as stronger predictors of HIV pathogenesis than CD4 T-cells count and viral load [65, 70]. This highlights the important role oxidative stress, inflammation and immune activation plays in apoptosis of CD4 T-cells in asymptomatic HIV infection. As a result, this knowledge or understanding of oxidative stress-induced inflammation, immune activation mechanisms, processes in the two diseases hold the key to better understanding of carcinogenesis. Importantly, targeting signaling pathways involved in activation of these processes might provide ideal and novel therapeutic targets. Besides, modulation of oxidative stress-induced inflammation and immune activation using selected antioxidants had been shown to protect or inhibit CD4 T-cell death in asymptomatic HIV infection [8]. In support of this, *N*-acetyl cysteine (NAC), a vital thiol antioxidant, has been shown to influence telomerase activity, inhibiting senescence in cancer cells [88]. Likewise, the daily use of small doses of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) was shown to decrease cancer risk [89], implying that oxidative stress, inflammation and immune activation are active participants in carcinogenesis.

This therefore demands a paradigm shift in our thinking, to start appreciating more the role played by these “drivers”, focus more future research on them, their specific role or as cancer therapeutic targets and preventive strategies. Previously, oxidative stress, inflammation and immune activation were thought of as consequences but not causes of cancer. However, results of this descriptive review, supported by several earlier studies strongly suggest a causal association. Therefore, future studies, both in vitro, retrospective case-control studies focusing specifically on causal association of oxidative stress, inflammation, immune activation and cancer, their mechanistic actions, how to target their activation, signaling, modulation as therapeutical targets and preventive strategies are urgently required. The author concurs with previous authors [76], that some of the cancer hallmarks such as resistance to cell death (apoptosis), replicative immortality, metabolic reprogramming and clonal selection could probably be cellular adaptations to chronic oxidative stress.

As a recommendation, the role of ROS, oxidative stress-induce inflammation and immune activation in induction of metabolic reprogramming, persistent signaling of NF- κ B, Ras, c-Myc, p53, Rb, anti-apoptotic gene Bcl-2, DNA damage, resistance to cell death, induction of “driver mutations” in proto-oncogenes and inactivation of tumour suppressor genes need to be exhaustively investigated. Notably, majority of the current cancer chemotherapies are limited in their action and ineffectiveness as they target single pathway, enzyme, indiscriminately kill tumour as well as normal cells, hence the many and serious adverse reaction

associated with them. Therefore, the main future challenge, will be designing a safe, potent combination or a “magic bullet” capable of discriminating between cancers, normal cells, kill the cancer cells, working on several targets, signaling pathways, receptors and an efficient delivery system of the therapeutic formulations. A limitation of this study was that only three databases that were searched due to inaccessibility of others such as Medline and Scopus as a result of lack of subscription.

5. Conclusions

Cancer and asymptomatic HIV infection share important similarities and differences. Understanding of what drives these specific but essential similarities and differences in the two diseases might provide new mechanistic insights in carcinogenesis, provide future therapeutic targets, inform policy on cancer prevention, screening and early diagnosis. However, more studies including in vitro studies, retrospective case-control studies, focusing specifically on the role of these key drivers in carcinogenesis, cancer maintenance and progression are required to strengthen the hypothesis. In addition, information from this descriptive review will help in stimulating more research interest in the field, accelerate discovery of future novel therapeutic targets and preventive strategies. This will have a direct impact on cancer treatment, management and prevention. This will helping in attainment of the United Nations SDG number 3 on ensuring healthy lives and promotion of wellbeing for all at all ages and most importantly Kenya’s vision 2030.

Conflict of Interest

The author declares no conflict of interest in conducting and publishing this review.

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