

Review

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# Hepatocellular carcinoma in Hepatitis B and Human Immunodeficiency Virus coinfection in Africa: a focus on surveillance

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## Abstract

Human immunodeficiency virus (HIV) and hepatitis-B virus (HBV) infections are weighty public health challenges, especially in the African continent. The direct carcinogenic effect of HBV means that it remains a potent cause of early-onset hepatocellular carcinoma (HCC) in Sub-Saharan Africa (SSA), where it causes significant morbidity and mortality. The presence of HIV infection in HBV-infected patients poses a complicating factor, as coinfection has been shown to hasten the progression of liver disease to cirrhosis and HCC, and often resulting in early-age hepatocarcinogenesis with consequent late diagnosis and lower survival. In this review, we discuss this unique conundrum, the epidemiology of HIV-HBV coinfection in SSA, its effect on liver disease and development of HCC, as well as practices and barriers to HCC surveillance in this distinct population. We propose a way forward to curb this considerable health burden focusing on reduction of disease stigma, the need for easy-to-measure biomarkers, and implementation of large prospective studies in this population.

**Keywords:** HBV, HIV, coinfection, hepatocellular carcinoma, surveillance, Sub-Saharan Africa



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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third cause of cancer-related mortality worldwide, with a large proportion of these deaths occurring in Africa<sup>[1]</sup>. HCC typically develops in the context of liver cirrhosis secondary to underlying chronic liver disease. Chronic infection with Hepatitis B virus (HBV) is the leading cause of HCC, causing more than half of the world's HCC deaths<sup>[2]</sup>. Infection with the human immunodeficiency virus (HIV) is also a major public health hazard across the world<sup>[3]</sup>. HBV and HIV coinfection is relatively common in endemic areas due to their similar transmission patterns, and previous research has demonstrated that these diseases can lead to worse overall outcomes when co-existing in a patient<sup>[4]</sup>. Moreover, beyond coinfection with HBV, HIV-positive individuals are at a higher risk of developing HCC compared to the HIV un-infected population and can do so at earlier ages<sup>[5]</sup>. Africa and East Asia are estimated to account for more than 75% of global HCC patients<sup>[6]</sup>. Indeed, unique risk factors, such as a high prevalence of HIV in the context of HBV or hepatitis C (HCV) coinfection, as well as exposure to aflatoxins and underreported consumption of alcohol help explain the high incidence of HCC in these regions<sup>[6-8]</sup>. Moreover, the dynamics related to poor outcomes in HCC are increased in resource-limited settings including many parts of Africa, where most of HIV infections occur<sup>[9,10]</sup>. Surveillance for HCC, aimed at early detection and implementation of tumor cure, brings novel complexities when related to HIV-infected individuals. Indeed, recent studies show that ultrasound surveillance has a low performance for HCC in HIV-infected individuals, with a suboptimal 43% rate for early-stage diagnosis, compared to ~63% found in studies in non-HIV-infected cohorts<sup>[11,12]</sup>. Thus, the burden of HCC in HIV and HBV-coinfection as well as the lack of effectiveness of ultrasound for early detection of HCC in these patients all intersect in complexity further augmenting morbidity and mortality in this population. In this review, we aim to address the need and critical role of surveillance of HCC in HIV and HBV coinfecting populations, with a focus on the African region.

## HIV-HBV COINFECTION

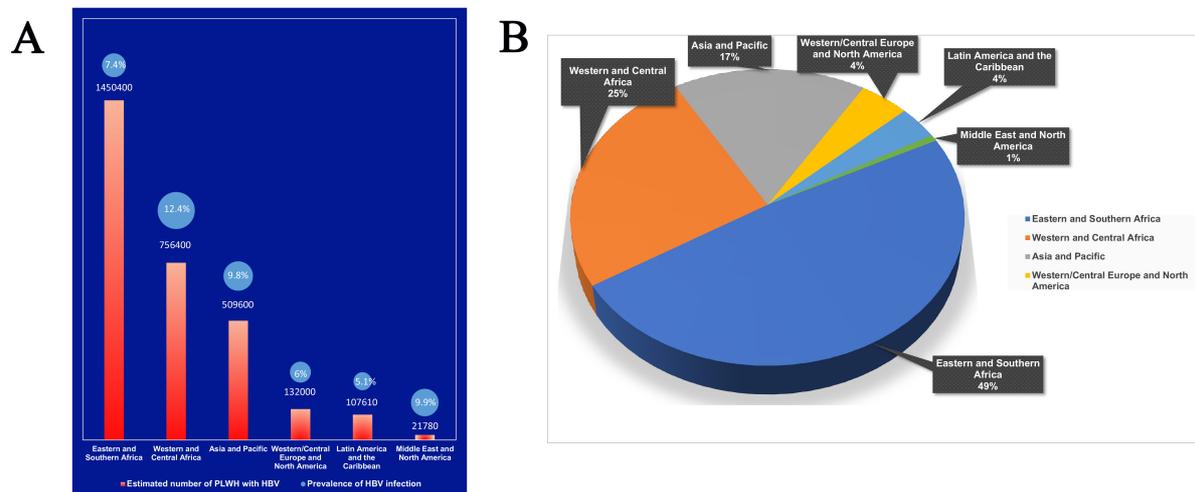
### Overall epidemiology

According to a report in 2005, an estimated 2-4 million people infected with HIV are also chronically infected with HBV<sup>[13]</sup>. A 2020 meta-analysis showed an estimate 8.4% coinfection rate of HBV in People Living with HIV (PLWH), with a quarter of those patients having active transmission of the virus<sup>[14]</sup>. The proportion and risk factors of HBV-HIV coinfection differ considerably based on geographical location [Figure 1A]. Due to common transmission channels and associated risk factors, chronic HBV infection in PLWH is more common in areas where both viruses are prevalent, with 74% of estimated regional HBV cases in PLWH coming from Sub-Saharan Africa (SSA) and 17% from the Asia-Pacific region<sup>[14]</sup> [Figure 1B]. Because of perinatal and early childhood transmission patterns, SSA accounts for the majority (65%) of HIV infections worldwide and has a higher incidence of chronic HBV infection<sup>[14]</sup>.

### HIV-HBV coinfection epidemiology in Africa

The World Health Organization (WHO) African Region is the region most affected by HIV in the world, with 25 million people living with the virus. This region does not only rank the highest in prevalence, but it also has the highest number of new infections, at 1.1 million people in 2018. The countries with the highest rates of HIV in Africa include Eswatini, Lesotho, and Botswana. In 2020, Eswatini had the highest prevalence of HIV with a rate of almost 27%<sup>[15]</sup>. Looking at coinfection, from a total of 37 million people who were infected with HIV, 2.7 and 2.3 million people are estimated to be coinfecting with HBV and HCV, respectively<sup>[16]</sup>.

Among countries in SSA, there is significant variability in the prevalence of HBV/HIV coinfection. A study from Ethiopia determined the HBV/HIV coinfection rate at 5.5%, somewhat similar to that in Uganda at



**Figure 1.** Regional estimates of Hepatitis B Virus infection in People Living with Human Immunodeficiency Virus (PLWH). All the data in the charts were obtained from Leumi *et al.*'s publication<sup>[14]</sup> in 2020. Note: Eastern Europe and Central Asia's data is not available. (A). Estimated number of PLWH with HBV infection in different regions of the world and the prevalence of HBV infection in PLWH. (B). Proportion among total regionally estimated HBV infection cases in PLWH. Note: Sub-Saharan Africa (Western, Central, Eastern, and Southern Africa) = 74%

6.7% and in Tanzania's at 6.6%. In contrast, some reports expose higher coinfection rates in other countries such as Sudan (14%) and Cameroon (25%)<sup>[17-21]</sup>. A systematic review by Stabinski *et al.*, including 81 studies worldwide, revealed that HIV/HBV coinfection rates differ greatly across SSA<sup>[22]</sup>, varying from 0% to 28% with a median of 7.8%. However, most of the studies described above are not from standardized population-based surveillance, so the estimates may not reflect the full population prevalence. A recently published meta-analysis including 314 studies (1999-2022) by Kenfack-Momo *et al.* calculated the HBV seroprevalence at 10.5% in PLWH in Africa<sup>[23]</sup>. A subgroup analysis showed that the top three countries in terms of HBV prevalence in HIV were Burkina Faso (14.7%), Nigeria (13.3%) and Ivory Coast (13.1%). It is important to note that substantial heterogeneity exists since the prevalence were estimates calculated from multiple studies<sup>[23]</sup>.

### The effect of HIV-HBV coinfection on the liver

HIV can affect HBV and liver Physiology in various ways. The presence of HIV infection may increase transmission and reduce control of HBV. In mothers infected with HBV, transmission from mother to child is aided by the presence of HIV<sup>[24]</sup>. Moreover, HIV is a risk factor for reactivation of HBV, particularly in patients with severe immunosuppression<sup>[25]</sup>. There is also evidence showing that interaction between HIV and HBV reduces the ability to eliminate HBV infection after exposure, resulting in increased HBV DNA concentrations, which in turn, leads to rapid progression to fibrosis and HCC<sup>[26]</sup>.

There is also a direct effect of HIV on HBV and liver physiology. Recent research has linked rapid progression to cirrhosis from a direct impact of HIV on stellate cells, which play an essential role in the development of liver fibrosis<sup>[27,28]</sup>. The poor clearance of HBV due to the presence of HIV may potentiate the deleterious effect of unchecked HBV replication. It has been shown that HIV-HBV coinfection results in higher morbidity and mortality than HIV infection alone, thus lending credence to a synergistic effect<sup>[29]</sup>. Also, when compared to their HIV-negative counterparts, people with HIV-associated HCC present at younger ages, implying a shorter latency to hepatocarcinogenesis. Furthermore, those who are HIV and HBV coinfecting, particularly those with low CD4+ cell numbers, are at an elevated risk of liver-related death<sup>[30,31]</sup>.

Finally, treatment of HIV may affect HBV and liver physiology. Antiretroviral therapy (ART) has improved HIV patient survival by extending life expectancy. An expected consequence of this, is the dramatically increased risk of developing complications from other associated chronic diseases, such as cirrhosis and HCC<sup>[32]</sup>. Patients on ART, on the other hand, have a higher risk of hepatotoxicity after starting the therapy<sup>[33]</sup>. Novel ART has decreased the toxic effect of these medications in the liver. Indeed, the use of new therapeutic agents in combination with tenofovir (the most commonly used antiviral against HBV in PLWH) have less deleterious effect on steatosis and they are thought to potentially decrease risk of HCC by decreasing the risk of cirrhosis. Nonetheless, the specific effect of ART on HCC has not been well studied and many countries in Africa still use relatively older treatments which can increase the risk of liver dysfunction<sup>[23,34]</sup>.

## HEPATOCELLULAR CARCINOMA

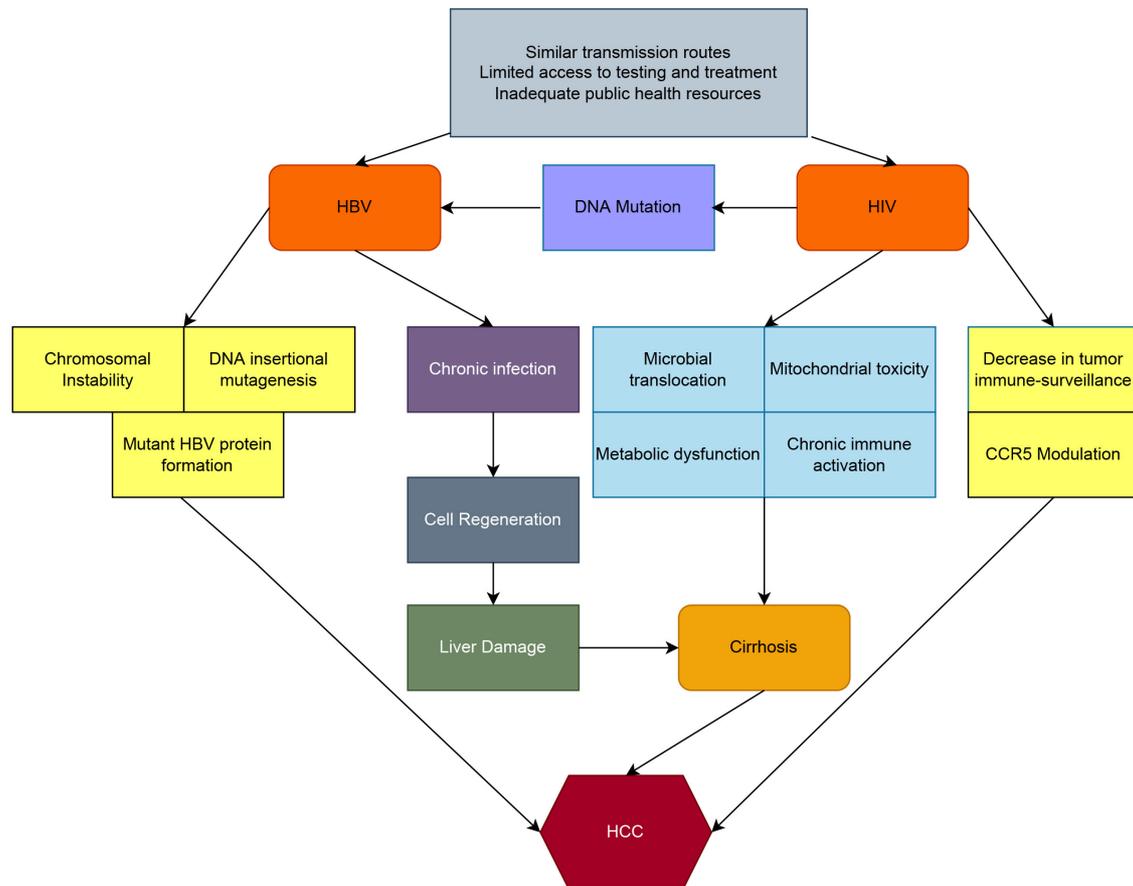
### HCC in people with HIV infection

PLWH have an increased risk of malignancies, often termed HIV-associated cancers. A registry linkage study of over four hundred thousand PLWH documented 21,294 incident cancers with a standardized incidence ratio of 1.69<sup>[35]</sup>. Moreover, three specific malignancies - Kaposi sarcoma, invasive cervical cancer and aggressive B-cell non-Hodgkin lymphoma are AIDS-defining cancers<sup>[36]</sup>.

The increased cancer incidence in people with HIV is related to multiple considerations. Firstly, HIV infection results in a loss of immune function and poor regulation of B-cells, leading to poor response when infections with oncogenic viruses occurs. This, in addition to the chronic B-cell activation seen even in controlled HIV infection may be responsible for development of lymphomas<sup>[37,38]</sup>. Secondly, a few oncogenic viruses have a similar mode of transmission to HIV. Such oncoviruses include HBV and HCV. Finally, as mentioned above, the improved care of patients with HIV has resulted in patients living longer with typical malignancies such as colorectal, breast and prostate cancer being seen more frequently in these group of patients<sup>[39]</sup>.

HCC remains an important cause of morbidity and mortality worldwide and it is associated with multiple diverse etiologic factors, especially HBV and HCV<sup>[40]</sup>. In PLWH, HCC is thought to occur at increased rates even without any underlying liver disease<sup>[41]</sup>. A large study using the national Veterans Health Administration Database, compared subjects with HIV alone with those with HIV-HCV coinfection and found that the presence of HCV dramatically increased the risk of development of cirrhosis and HCC<sup>[42]</sup>. The effect of HCV on the development of HCC in patients with HIV was also shown in a study of three cancer registry databases in Italy<sup>[5]</sup>. In SSA, it is thought that the prevalence of HBV infection in PLWH who develop HCC is even more pronounced<sup>[10,40]</sup>. Furthermore, a case-controlled study conducted in referral hospitals of four countries across West Africa revealed an adjusted OR of 2.2 [95%CI: 1.0-5.8] for HCC in HIV indicating a significant correlation between HIV infection and primary liver cancer<sup>[43]</sup>.

Multiple factors affect the pathogenesis of HCC in PLWH, especially in those with HBV [Figure 2]. The risk of coinfection with HBV is increased given the similar modes of transmission as alluded to earlier. More interestingly, there seems to be a difference in the pathophysiology of HCC in these patients. Defective CD4 and CD8 T-lymphocyte activity and immune dysregulation leads to unchecked replication of HBV in turn leading to early chronic inflammation, liver fibrosis and consequently, HCC<sup>[4]</sup>. This effect of HIV in the immune system has been buttressed by studies showing increased risk of HCC development in patients exposed to prolonged viremia and to extended periods of lower CD4 T-lymphocyte counts<sup>[44]</sup>.



**Figure 2.** Mechanisms and factors behind HBV-HIV coinfection in the development of cirrhosis and hepatocellular carcinoma in Africa. Flow chart detailing how similar routes of transmission and limited health resources increase the prevalence of HIV-HBV coinfection in Africa. HBV and HIV both induces cirrhosis by damaging liver cells by multiple mechanism, including chronic inflammation in the case of HBV and multiple metabolic alterations in the case of HIV. In addition, HBV by itself can also induce HCC in absence of cirrhosis by direct DNA mutagenesis thought to be related to viral insertion and HIV can increase the risk of HCC by itself by decreasing immune-surveillance (affecting NK cells) and by modulation CCR5, which has been involved in HCC formation.

Interestingly, differential modulation of CCR5 in HIV patients may allow the virus not only to enter CD4+ cells but also to attach to hepatocytes and cause pro-inflammatory and pro-fibrotic cytokine responses. A different study found that CCR5 inhibition dramatically lowers tumor load and fibrosis in a mouse model of HCC<sup>[45]</sup>. This data suggests that HIV may directly affect liver cells and induce HCC through modulation of CCR5<sup>[45]</sup>. Furthermore, reports suggest a more aggressive HCC phenotype in those with HIV as various studies have showed occurrence of malignancy in younger patients and often, at a more advanced stage of disease associated with invasive, infiltrating neoplasms and extrahepatic nodal metastasis<sup>[46,47]</sup>. Although the advanced disease and lower rates of survival may be related to a delayed diagnosis of HCC in these patients, a putative mechanism for aggressive tumor characteristics is likely the presence of HIV-induced growth signals that enhances HCC cell proliferation coupled with the inability of a weakened immune system to mount a potent anti-tumor response<sup>[5]</sup>. These phenomena call for a more proactive stance in the prevention and management of HCC in these patients. Interestingly, the majority of antiretroviral medications used to treat HIV have the inherent potential to be hepatotoxic. A study found out that cumulative use of stavudine (d4T), didanosine (ddI), and amprenavir (APV) was independently linked to higher risk of HCC<sup>[48]</sup>. However, other studies demonstrated that antiretroviral therapy's benefit on alleviating liver cirrhosis

outweighing their role in hepatotoxicity<sup>[49,50]</sup>. Finally, multiple studies have shown that genetic mutations related to increased risk of HCC are more common on HIV-HBV coinfecting patients<sup>[51,52]</sup>. Further details on mechanisms of hepatocarcinogenesis in this population can be found in other reviews<sup>[53,54]</sup>. Therapy for HCC in co-infected patients is similar to that of HIV-negative individuals. Moreover, liver transplantation which was in the past not available for this group of patients is now approved in many western countries<sup>[55]</sup>. However, transplantation is still beyond the reach of the great majority of the African continent.

### **HCC in HIV-HBV coinfecting patients in Africa**

A few studies from Africa attempting to explore the connections between HCC and HIV-HBV coinfection have been documented. However, they are limited in number and depth. A study from Mozambique found that 18% of HCC patients (34 cases) enrolled were infected with HIV, and the majority of these patients (68%) were coinfecting with HBV. In addition, HCC presented early in HIV-HBV coinfecting patients compared to HIV negative individuals<sup>[56]</sup>. A study from South Africa demonstrated that females with HIV-HBV coinfection present at a younger age (36 years) compared to HBV mono-infected women (50 years); more importantly, the HIV-infected patients had a lower median survival (82 days) compared to patients without HIV (181 days)<sup>[10]</sup>. Similarly, a prospective study carried out in a Hospital in Nigeria, showed that most patients with HIV and HCC were HBsAg positive, and at three months, the chances of survival in HIV-infected and HIV-uninfected individuals were 22% and 47%, respectively<sup>[57]</sup>. A recent report from Ethiopia by Tassachew *et al.* studied a large cohort of patients with liver disease and concluded that HCC patients had higher rates of HIV and HIV/HBV co-infection when compared to patients without HCC (8.6% vs. 1.8%) and (3.9% vs. 0.9%), respectively<sup>[58]</sup>. Interestingly, a separate study from West Africa suggested that HIV infection is not necessarily associated with HCC development<sup>[59]</sup>. All these studies need validation as they are quite limited in their sample size and have been performed in single geographic regions.

## **HCC SURVEILLANCE IN HIV-HBV COINFECTING PATIENTS**

### **Current HCC surveillance**

An effective cancer surveillance program aims to reduce cancer-related mortality. As it pertains to HCC, the main goal of surveillance is to detect HCC at stages where successful curative therapies can be applied. When compared to the general population, HIV-infected individuals have a five- to six-fold increased risk of developing HCC<sup>[60]</sup>. Therefore, it is crucial to establish an effective surveillance system in the HIV-infected population.

Surveillance for HCC is currently performed with ultrasound (US) imaging, with or without alpha-fetoprotein (AFP) measurement in blood; and it is recommended by liver and gastroenterology professional societies that this is done every 6 months<sup>[61]</sup>. All guidelines recommend initiating HCC screening for all African-origin HBV-infected patients at earlier ages, regardless of the presence of cirrhosis<sup>[61-63]</sup>. However, despite a thorough examination of the optimal screening frequency, there is a lack of compliance and adherence to this HCC surveillance guidelines in the overall population, as well as in the HIV infected population<sup>[40]</sup>. A variety of factors are likely to contribute to patients' poor adherence to HCC surveillance in HIV. Healthcare providers may lack knowledge of practice guidelines, and there may be a lack of a standardized system for scheduling and following screening examinations geared toward coinfection care<sup>[64]</sup>.

### **HCC surveillance studies in HIV-HBV coinfecting populations worldwide**

According to a cohort study carried on Paris in 2012, 61% of HCCs in individuals coinfecting with HIV and HBV were diagnosed during surveillance programs, compared to 85% of cases without HIV. Despite the difference not being statistically significant ( $P = 0.09$ ) this study does suggest a lower number of HCC diagnosed via surveillance in HIV-HBV coinfecting individuals than those with HIV alone<sup>[65]</sup>. Another study

in the UK looked at HCC surveillance in HIV-HBV coinfecting individuals of African Ancestry and found that only 24% underwent annual assessments and 7% underwent six-monthly assessments as indicated by the guidelines<sup>[66]</sup>. Similarly, a large European cohort of HIV/HBV/HCV coinfecting individuals with cirrhosis followed over a period of 10 years found a strikingly low adherence of between 5% and 18% to HCC surveillance guidelines<sup>[67]</sup>. Even though compliance with HCC surveillance standards increased marginally when the duration between US monitoring was prolonged to 12-month in the study, compliance rates remained low, at a maximum of 30%<sup>[67]</sup>. In another study from Canada, only 36% of HIV/HBV coinfecting patients seen in HIV practices completed HCC surveillance over a 2-year period, compared to 81% of HBV mono-infected patients seen in hepatology practices<sup>[68]</sup>. Sadly, poor compliance with surveillance adherence was linked to impaired liver function, more advanced tumor stages, larger nodules, and a lower chance of survival<sup>[65]</sup>. This study, however, should be interpreted with caution as the surveillance rate in HBV mono-infected was quite higher than most studies worldwide<sup>[68]</sup>.

Berretta *et al.* in a retrospective review study compared 104 HIV-infected patients and 484 uninfected patients with HCC<sup>[47]</sup>. The results showed that HCC was diagnosed more frequently through screening programs in HIV-uninfected patients than in HIV-infected patients. As expected, diagnosed while in a surveillance program was an independent factor associated with HIV patients' survival<sup>[67]</sup>. These and other studies, clearly show a decrease in surveillance adherence in HIV-infected patients when compared to HIV-negative ones. This is concerning when adherence rates for HCC surveillance are already low in HIV-negative cohorts.

#### **HCC surveillance in the HBV-HIV population in Africa**

Patients with HCC in Africa have among the lowest reported survival rates in the world, particularly when compared to patients from higher income countries<sup>[69,70]</sup>. A major contributor to this wide disparity in mortality is late presentation and diagnosis, in addition to a relative paucity of disease screening and HCC surveillance. There are no continental bodies or specific guidelines in Africa regarding HCC surveillance in patients with HBV with or without HIV, and approach to surveillance is usually performed by adapting guidelines from other continents. This leads to a lack of uniform approach that serves specific needs of the continent and therefore decreases the uptake on such guidelines. This in turn leads to less screening for HCC in at risk populations (as these populations are not clearly defined in Africa) and therefore late diagnosis. This issue is further aggravated in HIV-coinfecting populations. In addition, HCC in African patients can occur at a much earlier age, especially in HBV which makes up the etiology of underlying liver disease in up to 55% of cases<sup>[69]</sup>. Chronic exposure to aflatoxins - a common contaminant of grain products in SSA; and African iron overload syndrome - a consequence of local alcoholic beverage preparation; also contribute to the burden of HCC in this region and may further complicate the clinical course of those with HBV/HIV<sup>[71,72]</sup>. Late diagnosis, in turn leads to limited treatment options, as surgical resection, liver transplantation and curative ablative therapies are largely beneficial only in early stages of HCC<sup>[61]</sup>. Moreover, providers caring for PLWH tend to focus on infection-related issues, and frequently can "omit" the higher risk of HCC that this population has. These problems have been demonstrated in multiple studies across the region. A Ugandan study found that late treatment is responsible for high one-month mortality rate (73%), as monitoring for HCC in patients with cirrhosis is not routinely performed<sup>[73]</sup>. In South Africa, many HBV infections aren't discovered in PLWH until these individuals are diagnosed with HCC. As a result, many individuals appear with several lesions or large liver lesions on radiological examination, thus limiting the treatment options to palliative strategies<sup>[8]</sup>. Similarly, according to one study carried out in Egypt there is no efficient screening strategy for HCC in cirrhotic individuals with HIV, with only ~10% of new HCC detected during planned screening, while 38% of these patients had multiple liver tumors, and 72% had tumors greater than 5 cm in diameter<sup>[74]</sup>.

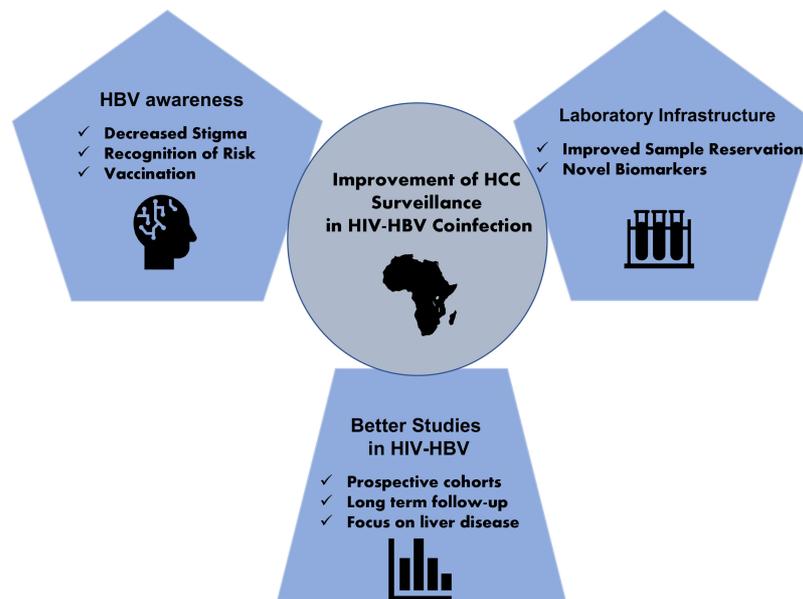
It is therefore conceivable that implementing strong surveillance programs in SSA will curb the poor outcomes associated with HCC in those with HBV/HIV. Recently, Riebensahm *et al.* performed a prospective pilot study where 303 HIV-HBV coinfecting adults undergoing ART were screened for HCC in two clinics in Zambia<sup>[75]</sup>. In this study, review of the ultrasounds showed that 24% of individuals had periportal fibrosis, 2% cirrhosis and 1% had liver steatosis. Liver lesions were found in 1.8 % of the individuals, but none of these individuals with liver lesions had an elevated serum AFP and not all liver lesions were HCC<sup>[75]</sup>. However, this study suggests that with proper organization, HCC surveillance is possible in this setting.

A myriad of problems affects HCC surveillance in patients with HBV/HIV. Two particular problems in SSA are that of cost and resource availability. Ultrasound is commonly accessible and less expensive, compared to other high-accuracy diagnostic imaging techniques such as computed tomography and magnetic resonance imaging. Nonetheless, adherence to surveillance is a concern due to affordability of multiple visits by patients. Another factor is the operator-dependent nature of ultrasound. The sensitivity of ultrasound in detecting early, small liver lesions is about 45% and so it is recommended that surveillance be carried out in specialized centers by well trained technicians and clinicians<sup>[76]</sup>. Although the potential provision of portable ultrasound machines offers an opportunity to mitigate problems associated with availability, we may still be besieged by issues surrounding technical manpower as training of personnel across the region requires a concerted and comprehensive effort<sup>[77]</sup>. In addition, most studies looking at ultrasound for HCC surveillance do not include HIV-HBV coinfecting patients, further undermining the potential of this approach in detecting early HCC. Patient hesitancy and distrust is also a considerable factor - an author of this paper once had a patient (in Africa) tell him that he did not like to go to the best imaging centers in town for surveillance because “they really try hard to find something in the liver”. These factors, either alone or in combination, make the implementation of a surveillance program in SSA very complex.

## FUTURE DIRECTIONS

Despite current recommendations, the implementation of ultrasound as surveillance strategy in HIV-HBV coinfecting individuals in Africa clearly falls far short of what is required. Moreover, despite AFP being the strongest studied biomarker, it is by itself insufficient for surveillance, particularly in the setting of HCC related to viral hepatitis, the most common underlying etiology in Africa. All these complexities are amplified by coinfection with HIV as very few studies have addressed either screening tool in this setting. The scientific and public health communities need novel, easy-to-measure biomarkers that could be easily implemented and used across different settings in these populations. A few novel biomarkers, such as des-gamma carboxy prothrombin (DCP) and lectin-bound AFP (AFP-L3), have shown promise<sup>[78]</sup>. These markers have been studied by itself or in combination with age and gender in what is called the GALAD score. Moreover, cell free DNA (cfDNA) - DNA released by tumor cells that can be detected in peripheral blood samples; has emerged as a novel tool with high potential. Indeed, methylation of several genes (i.e., HOXA1, TSPLY5, PFKP, *etc.*) in cfDNA have been shown to have a reasonable predictive value for HCC<sup>[79,80]</sup>. The combination of DNA mutations and cancer-associated proteins is a more exciting recent development in detecting HCC. In one study, a panel of four genes (TP53, CTNNB1, AXIN1, TERT), AFP, and DCP were used to distinguish HCC patients, with 85% sensitivity and 93% specificity in the training cohort<sup>[81]</sup>. An alternative group of biomarkers, include tumor associated antigens and antibodies such as squamous cell carcinoma antigen (SCCA) - and these biomarkers show potential, not only as a marker of early detection of HCC but may also help uncover new drug targets<sup>[82]</sup>.

Another promising method of early cancer detection is based on advanced imaging techniques. These include the use of artificial intelligence for digital extraction of high dimensional quantitative data from



**Figure 3.** Major changes needed to improve surveillance of HCC in HIV-HBV co-infected individuals in Africa. Flow chart describing the three aspects the authors deem necessary to improve HCC surveillance in HIV-HBV coinfection, including increased awareness of HBV disease, upgrading of laboratory infrastructure, and advancement of relevant cohort studies.

imaging<sup>[83]</sup>. Additional modalities to enhance imaging involve utilizing near-infrared indocyanine green fluorescence (NIRF) probes which bind to surface proteins, due to its faster uptake and deeper penetration depth<sup>[84]</sup>. These techniques may improve early radiologic characterization and diagnostic accuracy.

None of these biomarkers and modalities, however, have been studied in the HIV population. Moreover, the reproducibility of these tests and access to diagnostic equipment with enough capacity to measure them in resource-limited settings represent a substantial problem.

Overall, three major changes are needed to improve surveillance of HCC in HIV-HBV coinfected individuals [Figure 3]. First, awareness of the risk of HCC imposed by HBV, with or without HIV should increase dramatically continent-wide. Some countries have shown an important progress in these areas with awareness stimulation in television and radio programs, as well as outreach in rural regions<sup>[85,86]</sup>. However, further work in this area is critical to decrease stigma, increase understanding of the risks of HBV and improve vaccination rates, with reach of vaccination to rural areas as well as implementation of HBV birth-dose. Second, more investment in laboratory infrastructure should be considered. As biomarkers in blood become better and more accurate, samples are likely to become also more complex to process and more likely to require certain stability in the temperature chain when transporting. The African continent can benefit tremendously from novel biomarkers for HCC, and other cancers, but only if the proper infrastructure is present to implement them. Third, carefully designed, multicenter, well-controlled prospective cohort studies on HIV-HBV population focused on HCC are needed in the region. This is imperative, as most of the limited information on this lethal combination to the liver, originates in North America, Europe and Asia. Studies on HBV mono-infection show that the risk and features of HCC in Africa are quite different than that of the rest of the globe<sup>[87,88]</sup>. We should expect that the same is true for HIV-HBV coinfection and HCC. Therefore, proper studies specifically tailored for African populations and properly powered are a must.

All these changes needed for HCC surveillance improvement in HBV-HIV are reachable, and indeed scientists, governmental and non-governmental organizations are working tirelessly to achieve them. However, these important aspects will only show dramatic improvement when applied broadly in the continent, rather than in pockets of excellence.

## DECLARATIONS

### Authors' contributions

Write different sections of the manuscript: Wan Q, Anugwom C, Desalegn H

Development of figures: Debes JD, Wan Q

Conception, editing and overall warrantor of the manuscript: Debes JD

### Availability of data and materials

Not applicable.

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### Conflicts of interest

All authors declare that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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