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Review Article

Viral Hepatitis and Coinfections Burden, Trends, Risk Factors, Diagnosis and Treatment Strategies; Achievements and Challenges- Stakeholder Meetings, Narrative and Desk Reviews of The Zimbabwean Situation

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Abstract

Background: Despite the availability of effective vaccines and safer antiviral therapies, chronic viral hepatitis remains a major public health problem associated with the development of hepatocellular carcinoma (HCC). Tracking the burden and trends, particularly of hepatitis B (HBV) and C virus (HCV) that contribute ≥96% of all viral hepatitis mortality and morbidity is essential. **Methods:** We searched published articles in electronic databases, using keywords 'viral hepatitis', 'HBV', 'HCV', 'hepatitis D virus/HDV', 'hepatitis A virus/HAV', 'hepatitis E virus/HEV', 'hepatocellular carcinoma' and 'Zimbabwe'. Articles with at least an abstract available had data extracted and content analysed. A desk review of viral hepatitis standard documents and websites was done. Stakeholders' meetings were held to ascertain viral hepatitis preventive and curative strategies/practices in private and public health institutions. **Results:** Sixty-nine (69) articles were published between 1975 and 2022. Forty-nine (49) met the inclusion criterion; 9 and 40 being reviews and original articles, respectively. Of the original articles; 31, 5 and 4 were of cross-sectional, longitudinal and randomised-control-study designs, respectively. The 2022 Zimbabwe National Cancer Registry Report (ZNCR) indicated that out of the 7874 cancer cases recorded in 2018; 3% involved the liver. These contributed 7% of all the 2743 cancer deaths, disproportionately affecting adult black males; 5% versus 2% in females. Twelve (24.5%) studies mostly done over 25 years ago investigated HCC burden, diagnosis including risk factors. HCC was most prevalent in young adults' median 45 years, with a median survival of 2.5 months following first presentation. Risk factors included HBV/HCV infection(s), aflatoxin B1 exposure, high alcohol consumption, iron overload and metabolic dysfunction-associated fatty liver diseases. Twenty-two (44.9%) publications reported on viral hepatitis mono/coinfection(s) in rural, peri-urban and urban settings. Populations investigated included the general population, pregnant/lactating women, infants/children, non-remunerated-blood-donors (NRBDs), health professionals, out/

hospitalised patients and people-practicing-non-traditional-sexual-relationships (PPnTSRs). Criminal Law Act 2006 criminalises homosexuality. HBV prevalence fell from >40% before the 1990s to ~3% around 2022 with the burden remaining relatively high in the HIV-infected and PPnTSRs. Unusual HBV serology patterns were observed in 14% of HIV-infected immunosuppressed adults initiating Tenofovir and Lamivudine as part of combination antiretroviral therapy. Five studies (10.2%) investigated HBV transmission. Vertical transmission rates were <1%. Maternally HBV-exposed-babies tended to be born prematurely. HBV molecular epidemiological and qualitative studies on knowledge-attitude-practices constituted 6.1% and 4.1% of the studies, respectively. Occult HBV data was lacking. Molecular diagnostic facilities were non-existent. A 1988 study observed an HDV sero-positivity rate of 16.2% in hospitalised patients with acute HBV infection. Anti-HCV-antibodies seropositivity rates were 0.005% in NRBDs in 2018, ~1% in HIV-infected individuals in the 2000s. Frequencies were 1.6% and 24% in pregnant women and hospitalised HCC patients in the 1990s, respectively. Contemporary data on HCV are yet to be described. Five studies (10.2%), investigated the efficacy of different antiviral treatment regimens in HBV/HCV-mono/coinfection(s).

There was a dearth of information on oral-faecal viral hepatitis, particularly HEV. A 1984 study observed an HAV sero-prevalence of 31.2% in hospitalised patients with acute-HBV infection. The desk review identified 23 key standard documents; acts/policies, guidelines, strategic plans, technical reports, an essential drug (medicine) list for the most common health conditions in Zimbabwe (EDLIZ), the Zimbabwean Constitution, ZNCR, health professionals' curricula for nurses, medical doctors, laboratory scientists and pharmacists. According to the Zimbabwean Public Health Act (Chapter 15:17 of 11/2018) viral hepatitis is a notifiable communicable disease. Health professions curricula cover viral hepatitis topics. The EDLIZ 2020 edition recommends Tenofovir once daily for life for HIV-uninfected adults with chronic HBV. In the absence of this single formulation Tenofovir/Lamivudine combination is recommended. Once daily Sofosbuvir for 12 weeks is recommended for chronic HCV infections. Preventive strategies include infant hepatitis-b-vaccination with a coverage >83%, blood/blood-products and injection/sharps safety measures. Two stakeholders' meeting were held at the Ministry of Health HIV/Tuberculosis Unit and in Immunology Department, The University of Zimbabwe. Of concern were the non-existence of HBV/HCV diagnosis and monitoring algorithms, including standardised treatment endpoints. Due to the public health sector underfunding, administration of hepatitis-b-vaccine at age 6 weeks old rather than at birth remains a concern. National viral hepatitis surveillance and monitoring systems are yet to be established. Viral hepatitis screening of pregnant women was not universal. For sustainability, viral hepatitis control could be integrated into the successful ongoing HIV/AIDS programme. **Discussion:** HCC occurred in significantly younger productive age groups, thus negatively impacting economic development. HCC burden figures could be much higher as some patients may not present for treatment due to financial constraints or religious beliefs with some deaths occurring at home, hence unregistered. Oral-faecal-transmitted viral hepatitis studies were rare despite most cities' decades' long water and sanitation challenges. Molecular diagnostic facilities inadequacies may imply that viral hepatitis burden is underappreciated. HBV/HCV prevalence drastically fell over the past 50 years, courtesy of sound policies, guidelines and curricula. Evidence is suggestive of Zimbabwe being on course to meet the global targets aligned with the Sustainable Development goal number 3, aiming to eradicate HBV epidemic by 2030, reduce new infections by 90% and mortality by 65%.

Keywords: Viral hepatitis and hepatocellular carcinoma burden trends; Polices and implementation; Equity and financing; Health professionals' curricula; Population awareness; Preventive and curative strategies; Diagnostic algorithms and treatment end points; Monitoring and surveillance.

Abbreviations: AFP: alpha-feto protein; AGYW: Adolescent girls and young women; ALT: Alanine transferase; ART: Antiretroviral therapy; EASL: European Association for the Study of the Liver; EDLIZ: Essential drug (medicine) list for the most common health conditions in Zimbabwe; HAV: Hepatitis A virus; HBcAg: Hepatitis B virus core antigen; HBeAg: Hepatitis B virus early antigen; HBV: Hepatitis B virus; HBxAg: Hepatitis B virus x antigen; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HDV: Hepatitis D virus; HEV: Hepatitis E virus; HIV: Human immunodeficiency virus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; MMR: Maternal mortality rate; MoHCC: Ministry of Health and Child Care; NBTS: National Blood Transfusion Services; NRBDs: Non-remunerated-blood-donors; PLWHA: People living with HIV and AIDS; PPnTSRs: People-practising non-traditional sexual relationships; SDG: Sustainable Development Goals; SSA: Sub Saharan Africa; TDF: Tenofovir; TTIs: Transfusion Transmissible Infections; WHO: World Health Organisation; ZNCR : Zimbabwe National Cancer Registry; ZDHS: Zimbabwean Demographic Health Survey

Background

Zimbabwe is a land-locked Southern African country with a total land area of 390757 km^2 sharing borders with Zambia, South Africa, Mozambique and Botswana/Namibia to the north,

south, east and west, respectively. Following 15 years of civil war, Zimbabwe (formerly Rhodesia) gained independence from the colonial occupation by the British Empire in April 1980. The capital city formerly Salisbury, was renamed Harare. Zimbabwe has a population of 16 million with an annual growth rate of 2.1% [1]. It is a predominantly young nation with a population median age of 18.7 years [1]. At least 67% of the population lives in the rural areas [2]. The country has an agriculture-dominated economy. Extreme poverty of <US1.8 per day rose from 23% in 2011 to 38% in 2019, with urban poverty rising much faster compared to the rural areas [3]. Citizens' health-seeking behaviours and utilization of the formal health care system are influenced by their perceived quality of health care delivery, beliefs including marginal propensity to save money for health care services. The 2010 Parliamentary Portfolio Committee on Health report stated that >80% of Zimbabweans consult traditional healers for different ailments [4]. On the other hand, some apostolic church sects who strongly believe in supernatural healing powers through faith and prayer refuse uptake of conventional medicine, including childhood immunisations. The United Nations International Children's Emergency Fund (UNICEF) estimated that a fifth of the population belongs to this apostolic sect [5].

Zimbabwe is divided into 10 provinces, which are further sub-divided into 63 districts for administrative purposes. The health services system is centralised for policy, decision making, funds allocation, including recruitment of staff. A primary health care entry approach was adopted in 1980 with the health delivery services decentralised at primary, secondary, tertiary (provincial) and quaternary (central) levels. Complicated cases are referred to the next level of health care. The hyperinflation over the years has been characterised by high costs of living against low and stagnant minimum real wages. This steep economic downturn is also characterised by high unemployment rates with most families struggling to make ends meet. Challenging conditions of services in the health sector, such as aging equipment and infrastructure, limited supplies of basic medicines and personal protective equipment are common. Challenging conditions of services, hyperinflationary environment and poor remunerations have resulted in unprecedented outmigration of skilled and experienced health personnel to neighbouring countries, Europe, Australia and the Americas. This brain drain negatively affects the general health service delivery, since the public sector provides ≥65% of health care services, complemented by mission and private hospitals, including non-governmental organizations [6]. The excessive brain drainage of health professionals is happening at a time when the demand for health care services is increasing, a situation worsened by the recent emergence of the COVID-19 pandemic. Access to primary care physician is unavailable particularly in rural areas. According to the 2016-2020 National Health Strategy, none of the 10 provinces met the health facility density. The expected number of health facilities of 1 per 10 000 population is well below the national set target of 2, and so is the core health worker median density of 5 against national set target of 23 [7].

Zimbabwe faces a myriad of poverty related communicable and non-communicable diseases. This situation is compounded by the citizens' adoption of westernised diets and an increasing sedentary life style. Maternal mortality which refers to pregnancy or childbirth related deaths assessed per 100, 000 live births remains relatively high. Based on the Zimbabwean 2014 Multiple Indicator Cluster Survey, the maternal mortality ratio (MMR) was 614 deaths falling to 363 per 100 000 live births in 2021, against a national set target of 174 deaths per 100000 live births. Such trends are significant since MMR is an indicator of the overall general health of a population, the status of women in society and the barometer gauging the functioning status of a country's health delivery system [8]. The global Sustainable Development Goal (SDG) Target 3.1, 2016-2030 was developed with the aim to reduce the MMR to <70 maternal deaths per 100 000 live births [9]. On the other hand, the under 5 mortality rate was 75 and 49.5 per 1000 live births in 2014 and 2021, respectively, against a set target of 43 per 1000 live births [10,11]. The declining maternal-infant mortality figures are courtesy of new strategies ensuring that every pregnant woman receives at least some antenatal care, is attended to by a skilled birth attendant during labour, and that the mother and baby receive postnatal care within two days of birth.

Fifty percent of the population requires food aid, a condition worsened by climate change with ~650 000 (27%) children under five years of age suffering from chronic malnutrition; low-height-for-age or stunting [12]. According to the 2015 Zimbabwean Demographic Health Survey (ZDHS), 27% of the children were stunted, 3% wasted, 8% underweight and 6% overweight [13]. The deteriorating economic environment with no meaningful job creations in the economy, exacerbated by limited recreational activities/facilities, has seen adolescents and youths use illicit drugs and abuse alcohol as a coping mechanism for their frustrations.

HIV prevalence is at 13.8% among adults and 1.8% in children aged 0-14 years [13]. The country experienced a measles outbreak in 2022 with at least 7700 cases and 750 deaths recorded throughout the country [14]. The tuberculosis epidemic is largely HIV driven with a coinfection rate of 54% recorded in 2020 [15]. In addition to the HIV scourge, malaria, soil transmitted helminthes including the re-emergence of cholera and typhoid mainly due to the overstretched and dilapidated water and sewer infrastructure in the face of the ballooning city population growths has worsened the situation [16]. This is despite the Constitution in Section 77 providing for every person the right to safe, clean and potable water. Viral hepatitis burden is also on the increase. It is caused mainly by five viruses, and all can cause acute hepatitis. These include HAV, HBV, HCV, HDV and HEV. These hepatotropic

viruses attack the liver cells, hepatocytes, causing inflammation of the liver. HDV occurs only in the presence of HBV with HBV/HDV co-infection resulting in worse disease outcomes.

Blood borne viruses; HBV, HCV and HDV are the common causes of chronic hepatitis leading to progressive scarring of the liver (cirrhosis) and primary liver cancer, HCC [17]. HCC is the sixth most common cancer worldwide, yet in comparison to the other major infectious diseases, chronic hepatitis has not received the much needed attention. HCC and cirrhosis are of public health significance in Sub Saharan Africa (SSA) where mortality increased by 31% between 1990 and 2010 [18,19]. Globally, approximately 240 million people have chronic HBV infection with high to intermediate endemicity of 10-20%, primarily acquired during the perinatal period and early childhood in SSA [20].

HBV belongs to the Hepadnaviridae family characterised by enveloped viruses with an incomplete double-stranded DNA genome of 3.2 kb in size. Upon infection of the hepatocytes, the HBV nucleocapsid is transported to the nucleus where the relaxed circular HBV DNA is converted into covalently closed circular DNA that then serves as a transcription template for seven viral proteins [21]. These proteins include, a secreted dimeric early (e) antigen (HBeAg), viral capsid protein core antigen (HBcAg), polymerase reverse transcriptase (Pol/RT), large, medium and small surface envelope glycoproteins (PreS1, PreS2, HBsAg) and finally, a multi-functional non-structural x antigen (HBxAg) [22]. HBcAg is detected only in infected hepatocytes and not in serum. Anti-HBc-IgM antibody is detected during acute infection whereas the respective HBc-IgG antibody emerges 1-2 weeks following the presence of HBsAg. Anti-HBc-IgM antibody weans off after 6 months of acute infection with the anti-HBc-IgG antibody persisting both in resolved HBV infection and chronic HBV hepatitis. The presence of HBsAg in serum is the serological hallmark of HBV infection, and persistence beyond six months indicates chronic infection [23]. The new nomenclature of the natural history of chronic HBV infection is based on the description of the two main characteristics of chronicity: infection versus hepatitis according to the 2017 European Association for the Study of the Liver (EASL) guidelines [24]. The EASL guidelines take into account the presence of HBeAg, HBV DNA levels, liver enzymes alanine transferase (ALT) levels with the presence or absence of liver inflammation. The following are the described five phases;

1. **HBeAg-positive chronic HBV infection**: characterised by presence of serum HBeAg, high HBV DNA levels, normal ranges of ALT, and minimal liver necro-inflammation or fibrosis. It is common in perinatally infected individuals with preserved HBV-specific T lymphocyte function. Maternal positivity for HBeAg and the high HBV DNA load are the two most important risk factors predisposing to HBV intrauterine transmission [25-27].
2. **HBeAg-positive chronic hepatitis:** characterised by presence of serum HBeAg, high HBV DNA levels, elevated ALT, moderate/severe liver necro-inflammation and accelerated progression to fibrosis, common in individuals infected in adulthood.
3. **HBeAg-negative chronic HBV infection**: characterised by presence of serum anti-HBe, low HBV DNA (<2000 IU/mL), normal ALT levels and low necro-inflammation/fibrosis.
4. **HBeAg-negative chronic hepatitis:** characterised by detectable anti-HBe, persistent or fluctuating moderate to high levels of HBV DNA or ALT levels including necro-inflammation/fibrosis.
5. **HBsAg negative occult HBV infection (OBI):** characterised by serum negative HBsAg and positive anti-HBc with or without detectable anti-HBs is OBI. HBsAg and HBV DNA are not present in the serum but HBV DNA is detectable in the liver.

OBI occurs in 1%, 15% and 27% of HIV-infected individuals in the United States, South Africa, Botswana, respectively [28,29]. However, such information remains poorly described in Zimbabwe.

HCV is another important cause of chronic viral hepatitis common among injection drug abusers. It belongs to the genus Hepacivirus under the Flaviviridae family. It is a positive–sense single stranded RNA virus about 9.6 kilobases in size [30]. Due to its positive–sense properties, the viral RNA acts as the mRNA producing a single polyprotein that is cleaved to form several structural and non-structural proteins involved in viral replication and host cell pathogenesis [31]. Virus carriers remain asymptomatic for decades but are at risk of slow progression to severe disease and eventually death, unless treated timeously. Hence, HCV may be a public health threat in Zimbabwe, more so with the current upward trends in the use of illicit drugs/substances among adolescents and youths.

Like HIV, both HBV and HCV are blood borne viruses sharing the same mode of transmission through use of shared needles or sharps, horizontal and vertical transmission. Whilst HBV is a DNA virus that replicates in the nucleus, HCV is an RNA virus that replicates exclusively in the hepatocytes cytoplasm. However, both viruses have RNA replicative intermediates, hence theoretically they can interact in coinfected cells leading to different viral expression and serologic profiles. Four serologic profiles have been observed in coinfection being; co-dominant,

HCV dominant, HBV dominant, and neither replicative [32]. Such persistent viral hepatitis infections are characterized by host weak immune responses with subsequent development of ineffective CD8+ T-lymphocyte responses [33,34], a situation exacerbated by HIV infection endemic in SSA. HIV accelerates progression to cirrhosis and liver cancer, on the other hand, HBV infection has been associated with poor CD4+ T-lymphocyte recovery despite successful HIV-RNA suppression [35,36]. HBV, HCV and HIV coinfections pathogenesis are more complicated with treatments requiring administration of multiple antivirals simultaneously, a situation prone to development of drug resistance and hepatotoxicity, compared to single viral infections [37]. Understanding such dynamics is critical as co-infections are associated with faster immune deterioration, a situation exacerbated by the condition of pregnancy, which in itself is skewed towards Th2 profile [33,34]. Knowledge gaps exist on viral hepatitis epidemiology, coinfections dynamics, associated risk factors all critical for effective interventions and management. Tracking disease burden, trends, preventive including optimum and safer curative strategies, especially for HBV and HCV that both contribute ≥96% of all viral hepatitis morbidity and mortality remains essential. In addition, surveillance is critical for assessment of national progress towards the global target aiming to eradicate HBV and HCV epidemics by year 2030, reduce new infection by 90% and mortality by 65%.

Objective

This was a triad of a narrative literature review, desk review and summary of stakeholders' meetings aimed to comprehensively assess the situation of viral hepatitis burden, trends, risk factors, as well as prevention and curative strategies in place, and in the process identify the existing research gaps in Zimbabwe. This will ultimately guide future researches and direct policy through evidence based assessments of the past strategies versus the current situation on the ground with the aim to improve strategies to mitigate viral hepatitis burden.

Methodology

We searched published articles in electronic databases, using keywords 'viral hepatitis', 'HBV/hepatitis B virus', 'HCV/hepatitis C virus', 'HDV/hepatitis D virus', 'HAV/hepatitis A virus', 'HEV/hepatitis E virus', 'HCC/hepatocellular carcinoma' and 'Zimbabwe'. Articles with at least an abstract available had data extracted and content analysed. A desk review of viral hepatitis standard, related documents and websites was done. Stakeholders' meetings were held to ascertain viral hepatitis preventive and curative strategies/practices in private and public health institutions.

Results and Discussion

Original articles

Between 1975 and 2022 six-nine (69) viral hepatitis articles were published. Forty-nine (49) met the inclusion criterion; 9 and 40 being reviews and original articles, respectively. Of the original articles; 31, 5 and 4 were of cross-sectional, longitudinal and randomised-control study designs, respectively. Articles excluded were mainly those published before and during the 1970s without abstracts available. 22/49 (44.9%) studies were on viral hepatitis mono- and coinfection(s) burden in rural, peri-urban and urban settings done between 1984 and 2022. Population groups researched on included the general population, pregnant and lactating women, infants/children, non-remunerated-blood-donors (NRBDs), health professionals, outpatients, hospitalised patients with acute hepatitis and people-practising-non-traditional-sexual-relationships (PPnTSRs).

Meetings with stakeholders

Two meetings with stakeholders from the Ministry of Health and Child Care (MoHCC) partners, academia and private and public health care providers were held in November-December 2019. Discussions were around strategies and challenges around HBV control.

Desk reviews

The desk review identified the following viral hepatitis and related key documents;

i. Criminal Law Act 2006 (Section 73 on sodomy)

ii. Essential Drugs/Medicines List and Standard Treatment Guidelines for Zimbabwe (EDLIZ) 2020, 8th edition

iii. Globcan website

iv. Health professions curricula (for medical doctors, nurses, lab scientists, pharmacists)

v. Health sector waste management act for disposal of sharps

vi. Infection prevention and control (IPC) policy and guidelines

vii. Mental Health Act. Chapter 15:12 of 2016

viii. National Blood Services Zimbabwe (NBSZ) 2018 report

ix. Occupational Health & Safety Act; the Health Care and the Needle Safety Regulation

x. Parliament's 2010 health committee report

xi. Patient charter

xii. Report for the rapid assessment of viral hepatitis in Zimbabwe, June 2017

xiii. Strategic plan for the control and elimination of viral hepatitis in Zimbabwe 2019-2020

xiv. The Constitution of Zimbabwe Amendment. (No. 20) Act, 2013

xv. Traditional Medical Practitioners Act

xvi. University of Zimbabwe 2019-2025 strategic plan and research priority document.

xvii. Zimbabwe 2015 Demographic and Health Survey

xviii. Zimbabwean National Cancer Registry (ZNCR)

xix. Zimbabwe national infection prevention and control guidelines 2013

xx. Zimbabwe Public Health Act Chapter 15:17 of 2018.

Viral Hepatitis Acts, policies, strategies and guidelines

Zimbabwe is making progress in the prevention and control of viral hepatitis through the national strategic plan aiming towards ending the disease. This is in line with the Global Health Sector strategy on viral hepatitis 2016-2021; SDG 3 which aims to eradicate epidemics including HBV by year 2030, reducing new infections by 90% and mortality by 65% [38].

The Zimbabwe Public Health Act (Chapter 15:17) stipulates that viral hepatitis is a notifiable communicable disease. This Act empowers the MoHCC to protect the public health through regulating sanitation standards at restaurants, schools, and hospitals. The 2016-2020 National Health Strategy built on the 2009-2013 strategy that aims to address existing gaps and seeks to sustain the gains achieved to date through a comprehensive response to the burden of diseases, and strengthening of the health system to deliver quality health services to all Zimbabweans. The Government of Zimbabwe alongside stakeholders, partners and donors remains committed to the national response to sexually transmitted infection, including HIV and HBV.

In 2017 the MoHCC in collaboration with the World Health Organisation (WHO) commissioned a viral hepatitis rapid assessment to determine the national status on prevention, treatment, care and surveillance services with the aim to identify gaps post 2015 health agenda. For health governance, the MoHCC developed a National Health Strategy for 2009-2013 and the Patient's Service Charter. The 1996 Patients' Service Charter provides a basic framework on how patients should be treated throughout the health system by clearly defining the responsibilities of the clients as patients to attain the best possible curative and preventive services. The Constitution of Zimbabwe explicitly provides for the right to health care in Section 76, subsections 1-4. It states that every citizen has the right to access basic health care services, and no person should be refused emergency medical treatment at any public health care institution. The MoHCC through the National Blood Transfusion Services (NBTS) policy aims to safeguard the notion that receiving safe blood is a human right. Viral hepatitis has been labelled a neglected public health challenge on the increase during a stakeholder consultative meeting. Viral hepatitis was not included in the University of Zimbabwe 2019-2025 strategic plan and research priority document. In the meeting it was highlighted that there were clear policy documents, guidelines and instruments, but inadequate enforcements and practical actions to convert these excellent frameworks into efficient self-sustaining local practical solutions for the effective HBV and HCC control.

Hepatocellular carcinoma burden

The ZNCR was founded in 1985 following a collaborative research agreement between the MoHCC and WHO International Agency for Research on Cancer with the aim to gather statistics on cancer incidence and deaths.

The desk review identified two main source documents on HCC; the ZNCR and Globcan website. The ZNCR mandate is in line with the endorsed 2016-2021 Global Health Sector Strategy that tracks the progress of five cancer controls. These include strategic information, interventions, equity, financing and innovation as key pillars for monitoring progress and measurement of the impact of intervention on reducing new cases and saving lives between 2015 and 2030 [38]. Cancer mortality data is obtained mainly from death certificates at the Registrar General's office. Incidence data on the sequelae of viral hepatitis are obtained from radiotherapy records, including cytology, pathology and haematology reports from public and private laboratories nationwide.

Liver cancer has constantly been among the top 10 causes of cancer mortality since 2002. According to the 2018 ZNCR annual report published in September 2022, a total of 7874 cancer cases were recorded nationwide. Of these 3% involved the liver. Liver cancer mortality constituted 7% of all the 2743 cancer deaths recorded, disproportionately affecting adult males; 5% versus 2% females in black Zimbabwean population [39]. The Globcan website ranked liver cancers as number 7 out of the 35 cancers recorded in Zimbabwe in 2020; 678 and 648 new cases and deaths, respectively. New liver cancers cases constituted 6.1% of all cases recorded in 2020 [40]. Despite collating the liver cancer cases, the aetiology remains to be elucidated. The total numbers of new cancer cases and deaths recorded by the ZNCR and Globcan website could be an underestimate as many cancers may not be captured by the routine National Health Information System as some patients do not present for treatment due to financial constraints or religious beliefs. Furthermore, some deaths occur at homes, hence may not be registered.

Out of the forty-nine (49) researches that met the inclusion criterion, twelve (24.5%) were HCC original researches published between 1975 and 1997. All were of cross sectional study designs with sample sizes ranging from 17-182 mainly targeting hospitalised patients, Table 1. The most recent HCC study was published as long back as 2009 (9). Thus, contemporary data on HCC are yet to be described.

Timing of data collection	Study setting and design/type of document	Study population	Hepatitis Virus studied	Sample size	Main findings	Reference
Hepatocellular carcinoma (HCC) reviews (2)						
2022	Sub-Sahara Africa (SSA)	Adults	HCC burden	Not stated	HCC most prevalent in young adults' median 45 years, with a median survival of 2.5 months after presentation. Major risk factors for HCC, hepatitis B virus (HBV), hepatitis C virus (HCV), aflatoxin B1 exposure, and alcohol consumption, with metabolic dysfunction-associated fatty liver disease slowly emerging as a risk factor over the past few years.	[41]
2020	Central, West, East, and Southern Africa.	HCC patients	Incidence and mortality of liver cancer including HCC risk factors	Not stated	Incomplete adherence to birth dose immunization, lack of longitudinal follow-up care, and impaired access to antiviral therapy, aflatoxins exposure and, to a lesser extent, African iron overload. HIV/HBV co-infection increases the risk of developing HCC with lowest survival.	[49]
Viral hepatitis/ and coinfections prevalence reviews (4)						
2021	SSA	Survey of the members in the HCV SSA Network	HCV	25 senior treating physicians across 13 countries, heading of their national viral hepatitis programmes, and 13 blood transfusion services experts in 12 countries.	Most countries in SSA have multiple barriers to overcome before they can reach elimination targets. The cost of serological tests differs in each country, ranging from US$0·60 to $13 per test in Zimbabwe to $25 per test in Benin. In Zimbabwe, the cheaper serology tests are available only in public health facilities but often have a short supply of kits, forcing patients to seek tests in private facilities where costs are inevitably higher.	[105]
Articles published 2004-2019	SSA systematic reviews and meta-analyses, PRISMA standards	Pregnant women attending antenatal care	HBV/HIV co-infection burden	Not stated	Overall pooled seroprevalence of HBV/HIV co-infection was at 3.3%, with years 2004-2010 having higher prevalence of 6.3%.	[52]

1995	Africa	Africans	HBV pathogenesis and HCC risk factors	Not stated	African iron overload might be a risk factor for HCC	[170]
1990	SSA	General population	Overall hepatitis B surface antigen (HBsAg) seroprevalence	SSA	Carrier rate in the was 5-20%. Perinatal infection rate was 1-5% mainly through horizontal route. Mozambique had the highest incidence rate HCC of 103.8 per 100,000 males.	[60]
Viral hepatitis B vaccine (HepB) **related reviews (3)**						
1996	SSA review	General population	Overall prevalence of HBsAg	Not stated	High HBV carrier rates observed in the general population. Universal immunisation of all infants is recommended by incorporating HepB into the childhood Expanded Programme on Immunisation.	[59]
Articles published by 2015	Review	African children	Status of HBV control in the Africa	47 African countries	11 countries introduced HepB-birth-dose (BD); only nine provided universal HepB-BD, and of these, five reported ≥ 80% coverage. HBeAg prevalence among HBsAg-positive Zimbabwean women was 3.3%.	[120]
2020	Review	Reports, policy documents, guidelines including interviews with key informants	Viral hepatitis elimination strategies in place and challenges	12 documents reviewed, and interviews with 10 key informants	Strategies working well included screening of donated blood for transfusion, safe injection practices and three-dose HepB. Poor to non-existent were surveillance systems, lack of epidemiological data, absence of HepB-BD and lack of systematic screening and treatment services for viral hepatitis.	[171]
Original Research; Viral hepatitis and/or coinfections prevalence studies (13)						
2017-2019	Cross-sectional study using routinely collected data in the second largest city, Bulawayo	People living with HIV/ AIDS (PLWHA) initiating antiretroviral therapy (ART)	HBsAg-sero positivity rate	422	10% HBsAg-sero-positivity rate, associated with anaemia and elevated alanine transaminase levels.	[172]

2016-2019	Longitudinal study; from pregnancy until 2 years of infant age at four Primary health centres in Harare high density suburbs.	HIV-infected and HIV-uninfected pregnant women at least 20 weeks gestation and their infants	Antenatal HBV burden and adverse pregnancy/ infant outcomes in HBsAg-monoinfected and HIV/HBsAg co-infected	1208: 608 HIV-infected and 600 HIV-uninfected	Overall HBsAg-seroprevalence was 2.7% being 1.2% and 4.1% in HBsAg-monoinfected and HBsAg/HIV-coinfected, respectively. None of HBsAg sero-positive women tested positive for anti-HBs-antibodies in pregnancy, thus all women were vulnerable to HBV infection. In addition, none of the women were positive for the biomarker of viral replication HBeAg, with 47.9% women testing positive for anti-HBe-antibodies whilst 62.5% were positive for anti-HBc-total antibodies	Duri et al 2022 Under review
2017	Baseline analysis of a randomized controlled trial, in Harare	HIV-infected adults with advanced disease starting ART	HBV serological markers and plasma DNA concentrations	999	HBsAg positivity was significantly higher in Zimbabwe than Uganda; 12.2 vs. 7.7% despite comparable prevalence rates of antibody to HBV core antigen of 56.3 vs. 52.4% in the two settings. HBeAg was detected in 37% of HBsAg-positive patients, with higher rates observed in those with advanced World Health Organisation (WHO) HIV clinical stage. In HBsAg-positive patients, HBV DNA was undetectable in 21%.	[64]
2012	A cross sectional study at Parirenyatwa Group of Hospitals Opportunistic Infection Clinic; a large public sector Central Hospital clinic	HIV-infected ART naive adults	Co-infection with HBV and/or HCV	228	7.9% were HBsAg positive.0.9% were anti-HCV antibody positive. None of the participants were infected with both hepatitis viruses.	[70]
2010	Cross-sectional survey in rural, rural-urban and urban communities	Pregnant women	*Streptococcus agalactiae* colonization and coinfection with HIV-1 and/or HBV	369	HBV prevalence rates were 3.3%, 3.0% and 3.7% for rural, rural-urban and Harare urban, respectively. Single infections with GBS, HBV and HIV were 35.7%, 3.3% and 20.1% respectively. HBV/HIV coinfection was 0.8%.	[93]

2003	Cross-sectional survey in Rural Zimbabwe	General population	HCV	269; 145 HIV-uninfected and 124 HIV-infected adults	In this high HIV setting, HCV prevalence was 0.8% in the HIV-infected and none was infected in the HIV-uninfected group.	[62]
1999	Cross sectional study at Harare Maternity Central Hospital, Harare	Pregnant women	Sero-prevalence of HCV	1607	1.6% were anti-HCV antibody positive and was associated with maternal age.	[99]
1996 to 1997	Cross-sectional survey at Harare Maternity Central Hospital, Harare	Pregnant women	HBsAg seroprevalence and infectivity status	1000	25% women were carriers of HBV of whom 3.3% tested positive for HBeAg.	[97]
1996	Cross-sectional survey at National Blood Transfusion Service, Harare	Blood donors	Tests performances: a rapid assay to detect antibodies to HCV in serum and two rapid/ simple assays to detect HBsAg in whole blood or serum	206	The concordance between the two rapid HBsAg tests and the HBsAg ELISA immuno assay (EIA) was 99.5% and between the HCV-SPOT and the HCV EIA was 97.6%	[80]
1995	Cross-sectional survey at Rural Howard Hospital in Chiweshe District	Pregnant women attending an antenatal clinic	Prevalence of schistosomiasis, HBsAg and anti-HB antibodies.	299	*S. haematobium* and *S. mansoni* infection prevalence was 50%. Only 2% of the pregnant women tested positive for the two hepatitis B markers.	[94]
1989 to 1991	Cross-sectional survey in nine provinces of Zimbabwe	Adults and children; healthy population	HBsAg sero-epidemiology	1,461 males and 1,933 females in the age group 10-61 years	HBV was hyper-endemic in both rural and urban areas of Zimbabwe. Overall prevalence of HBsAg was 15.4%; in males being 16.8%, females 14.3%. Prevalence rates of HBeAg, anti-HBe, anti-HBs and anti-HBc were 25%, 25%, 45% and 36%, respectively. The prevalence of anti-HBs and anti-HBc increased continuously with age.	[61]
1988	Cross-sectional survey at Parirenyatwa Group and Harare Central hospitals	Acute HBV-infected patients	Detection of serum anti-delta (HDV) antibodies	130	An overall prevalence of 16.2%, being 19.6% in males. The seropositivity rates of HBeAg and anti-HBc were 49.2% and 89.2%, respectively.	[57]

1988	Cross-sectional survey in Harare	Hospital workers versus volunteer blood donor controls	Hepatitis markers	226 hospital workers versus 97 volunteer blood donor controls	131 (58%) hospital workers had hepatitis markers compared with 45 (46%) in the donor group. Racial group was the strongest risk factor. Blacks were 70% more likely to have markers than whites. This racial difference was not explained by job status or patient contact. Data suggested that working in a district general hospital does not constitute a clinically important hazard for HBV infection. Because of the high cost of the HepB vaccine, additional studies to assess the risk of hospital work in other settings in Zimbabwe were required before health policy regarding routine Heps B vaccination was recommended.	[76]
1987	Cross-sectional survey at a rural hospital in Zimbabwe	Outpatients	HIV/HBV sero-prevalence	401	Prevalence of HIV-1 antibodies in the Zimbabwe study population was 3.2%. All infections were found in the age group 17 to 30 years. Prevalence of HBsAg was 1.1%.	[69]
1984	Cross-sectional survey at an Infectious Diseases Hospitals in Harare	Admitted patients with acute hepatitis	Evaluation of anti-hepatitis A virus (HAV) antibody and anti-HBs antibody	141	HAV antibodies were present in 44 (31.2%, HBV in 86 (61%).	[56]
Original Research; Treatment of viral hepatitis and/or coinfections						

2011 2016	Clinical trial, multiple international sites	HIV/HBV coinfected women and adverse pregnancy outcome (APO)	Impact of ART regimen on APO/ infant outcomes randomized into (no anti-HBV)-zidovudine (ZDV) + intrapartum nevirapine and 1 week of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC); (3TC)-3TC + ZDV + LPV/r; or (FTC-TDF)-FTC + TDF + LPV/r.	138	The risk of APO increased with maternal ARV compared with ZDV alone, although the differences were not statistically significant. Maternal HBeAg was associated with a significantly increased risk of APO. Infant mortality was highest with FTC + TDF + LPV/r. Early assessment of HBeAg could assist in identifying high-risk pregnancies for close monitoring	[108]
2003-2004	Longitudinal study; follow up to 4.8 years	HBV/HIV-infected adults starting ART	166 were prescribed lamivudine-tenofovir and 58 lamivudine alone.	224	The suppressive effect of lamivudine alone was highly durable (up to 5 years) in HIV-HBV co-infected patients with baseline HBV DNA <6 log10 IU/mL. Authors suggested that it may be feasible to develop stratified approaches using lamivudine as the only drug with anti-HBV activity	[146]
2007-2008	Multinational cohort	HBV/HIV-co-infected patients receiving HBV-active ART either HBV monotherapy with either lamivudine or emtricitabine (N= 56), or HBV dual therapy with tenofovir disoproxil fumarate (TDF)/ lamivudine or emtricitabine (N=59).	Assessment of short and long-term HBV DNA suppression	115	The proportion with HBV DNA below 200 IU/ml was 60% at 24 weeks and 79% at 144 weeks. A higher proportion of HBeAg-negative patients (n = 57) achieved HBV DNA below 200 IU/ml at any point, regardless of the therapy group. All 12 patients with emergence of lamivudine-resistant mutants were in the monotherapy group.	[147]

2007 to 2010	SSA, randomized double-blind placebo-controlled trial of HBV perinatal transmission evaluated after 6 months of infant nevirapine versus placebo among breast-fed infants up until 18 months	Women living with HIV and their infants	Perinatal outcomes in HBV/HIV co-infection	2025	4.3% had HBV. HBV/HIV coinfected women with high HBV DNA load had lower median CD4, versus HIV alone. High HBV DNA load was associated with HIV perinatal transmission.	[109]
2003 to 2004	Longitudinal HBV DNA testing at 48 weeks and the last available sample before HBV-relevant modification of ART	Treatment responses in a cohort of HBV/HIV co-infected patients with detectable HBV DNA at baseline	HBsAg-positive patients were followed for up to 4.8 years	224; 166 were prescribed lamivudine-tenofovir, and 58 lamivudine alone.	The suppressive effect of lamivudine alone was highly durable (up to 5 years) in HIV-HBV co-infected patients with baseline HBV DNA <6 log10 IU/mL	[146]
HBV transmission studies and infant outcomes (5)						
2016-2019	Longitudinal; from pregnancy until 2 years of age at 4 Primary health centres in Harare high density suburbs.	HIV-infected and HIV-uninfected pregnant women at least 20 weeks gestation and their infants	HBV burden and adverse pregnancy/infant outcomes in HBV mono-infection and HIV/HBV co-infections	1208: 608 HIV-infected and 600 HIV-uninfected	HBV-exposed-babies tended to be born prematurely. No HBs-antibodies were detected at 2 years of age in 23.3% of HBsAg-exposed infants, despite having completed Hep B vaccination schedule, receiving the first dose at 6 weeks of age rather than at birth.	Duri et al 2022 Under review
2015	National Blood Service Zimbabwe	Non-renumerated blood donors	Cost effectiveness of introducing individual-donation nucleic acid testing (ID-NAT), in addition to serologic tests, compared with the exclusive use of serologic tests for the identification of HBV, HCV and HIV		ID-NAT in addition to serologic tests would lower the risk of HBV, HCV, and HIV transmission to 46.9, 0.3, and 2.7 per 100,000 donations, respectively. ID-NAT would prevent an estimated 25, 6, and 9 HBV, HCV, and HIV transfusion-transmitted infections per 100,000 donations, respectively.	[72]

2015	National Blood Service Zimbabwe	Non-renumerated blood donors	The Schreiber incidence-window period (IWP). IWP Model 1, an IWP amended version (Model 2) and the model to estimate the residual risk of transmission of infections by blood transfusion	Comparison of 3 model	The adapted NBSZ model provided comparable results to the published methods, and these highlight the high occurrence of HBV.	[79]
2007 to 2010	HIV Prevention Trials Network (HPTN) 046 randomized double-blind placebo-controlled trial of perinatal transmission that evaluated 6 months of infant nevirapine versus placebo among breast-fed infants	HBV/HIV coinfected women and infants	association between HIV-HBV coinfection and maternal and infant outcomes	88	There was no impact on infant mortality or maternal outcomes at 18 months. In HIV-HBV women, high HBV DNA loads increased the risk of low birth weight, potentially HIV perinatal transmission. Reduction of antepartum HBV viremia may have beneficial effects beyond the prevention of HBV perinatal transmission	[109]
1996 to 1997	Cross-sectional survey at Harare Maternity Hospital, Harare	Pregnant women	HBV carrier and infectivity status	1000	0.8% of the entire study population was found to be at high risk of transmitting HBV to their new-borns.	[136]
Original research; HBV molecular epidemiology (3)						
2014.	Cross-sectional survey in Harare	Adult patients	Molecular epidemiology of HBV/HIV co-infections	176	All isolates were sub-genotype A1 without HBV drug resistance mutations, HIV-1 subtype C and only one was HIV-1 subtype F1.	[65]
2011	Cross-sectional survey in Harare	Blood donors	HBV genotype distribution	29	Sub-genotype A1 HBV isolates	[77]
1992	Cross-sectional survey in Harare	Patients with acute HBV infection	Amplification of HBV pre-S1, pre-S2 and S gene sequencing regions	3	Greatest homology to the HBV adw subtype	[173]
Original qualitative studies: knowledge attitude and practice (2)						

2013	Cross sectional study in Harare was conducted using a structured 36 item interviewer administered questionnaire	Private and public dental practitioners	Knowledge, attitudes and practices of Harare oral health professionals regarding HBV in the workplace	89	Appreciated the risk of HBV transmission in dental settings, but with incomplete knowledge of HBV infection. There was poor uptake of HBV vaccination among these health professionals.	[83]
2006	Cross-sectional survey assessing the general infection control practices with special reference to the prevention of transmission	Dental therapists in Zimbabwe	Assessment of the general infection control practices	24	All were trained in Zimbabwe; 91.7% had not been vaccinated against HBV and only 20% had undergone previous HIV testing. Use of gloves was universal; 92% used face masks; 66.7% used protective eyewear; 87.5% wore protective garments; 95% autoclaved/chemoclaved high speed hand pieces; 83.3% autoclaved/chemoclaved slow speed headpieces. Barriers to infection control ranged from 22.7% to 40.9% and was attributed to non-availability of gloves and disinfectants. Dental therapists seem to practise acceptable infection control methods. There was need to improve upon headpiece sterilization, the use of eyewear and improvement upon supplies for disinfection. Vaccination against HBV needs to be encouraged.	[82]
Original research; HCC						
2009	A cross sectional study design at Parirenyatwa Central Hospital	Primary HCC patients	HBV and HCV	60	48.3%, 20% and 8% seropositive for HBV, HCV and HBV/HCV-Co-infections.	[53]
1997	A cross sectional study design at Parirenyatwa Central Hospital	HCC patients	HCV and HIV antibodies	63	Anti-HCV seropositivity rate was 23.8%, and present in 80% males. HIV antibodies were found in 28.8% of whom 70.6% were males. HBsAg was detected in 42.6%. Younger HCC patients had high prevalence of HBsAg and anti-HIV but a low prevalence of anti-HCV; while older patients had a high prevalence of anti-HCV but low prevalence of HBsAg and anti-HIV.	[42]

1995	A cross sectional study design at Parirenyatwa Central Hospital	HCC patients	Utility of fine needle aspiration (FNA) of the liver without ultrasound guidance in HCC patients.	110	FNA of the liver for the diagnosis of HCC is a safe, simple and accurate procedure which can be undertaken in settings that would otherwise not be suitable for formal liver biopsy. Dizziness observed in one patient.	[47]
1990	Westmead Hospital	Hepatic focal nodular hyperplasia (FNH) patients	A possible link between FNH and hepatic malignancy	17	FNH was found in association with HCC	[48]
1992	A cross sectional study design at Parirenyatwa Central Hospital	HCC patients	The interrelationship between HBV markers, HIV and HCC	282: 182 HCC patients and 100 control patients	64.5% HCC patients had detectable alpha-feto-protein (AFP) >1,000 ng/ml. 40.1% and 36.5% were positive for HBsAg and anti-HBc, respectively. HBeAg was present in 18.6% of the HBsAg positive patients. Anti-HIV antibodies were present in 5.3% of the 282 tested individuals. Only 1 (1.0%) within the control group had detectable anti-HIV antibodies in the serum. 11% and 4.0% of the same control group had HBsAg and anti-HBc antibodies in their sera, respectively.	[51]
1987	A cross-sectional study in a rural set up	Lactating women with primary HCC	Association between dietary exposure to aflatoxin (AF) incidence of primary HCC	54	Contaminated milk of levels of up to 40 pg AF per ml, 11% positivity rate. No positive samples were detected in control samples from France.	[55]
1977	Prospective survey of primary liver carcinomas	Black Rhodesians	Factors associated with HCC	28	Commonest presenting symptoms were abdominal pain and swelling and weight loss. Hepatomegaly, often tender and nodular, was present in all but one. The detection rate of AFP was 46.5% with HBsAg being absent in all 28, suggesting that there was no association between the persistence of the antigen and HCC. Liver function tests, although abnormal, were never diagnostic of primary liver cancer. Authors confirmed the association of high alcohol consumption with cirrhosis or HCC.	[43]

1977	A cross-sectional study in a Salisbury Professorial unit	Black Rhodesian patients with cirrhosis of the liver	Histology in liver cirrhosis	35	There was a complete absence of gynaecomastia, spider naevi and liver palms. Histologically, most patients had macronodular cirrhosis, and only 1 patient had micronodular cirrhosis with minimal fatty change. HBsAg was not detected in any patient, despite a positive HBsAg rate of 4% in Black African blood donors, determined by means of the same laboratory technique	[54]
1975	Cross sectional study in Rhodesia	Black Rhodesian patients with histologically proven hepatoma	Utility of AFP in diagnosis of HCC	30	Only 47% had AFP detected, necessitating the need for negative test results to have liver biopsy done in all patients with clinical suspicion of liver cancer.	[45]
N=49; 9 and 40 being reviews and original articles, respectively. Of the original articles; 31, 5 and 4 were of cross-sectional, longitudinal and randomised-control-study designs, respectively. **Abbreviations:** AFP: alpha-feto protein ALT: Alanine transferase, ART: Antiretroviral therapy, EASL: European Association for the Study of the Liver, EDLIZ: Essential drug (medicine) list for the most common health conditions in Zimbabwe, HAV: Hepatitis A virus, HBcAg: Hepatitis B virus core antigen, HBeAg: Hepatitis B virus early antigen, HBV: Hepatitis B virus, MoHCC: Ministry of Health and Child Care, NRBDs: Non-remunerated-blood-donors, PLWHA: People living with HIV and AIDS, SSA: Sub Saharan Africa, TDF: Tenofovir, ZNCR: Zimbabwe National Cancer Registry, ZDHS: Zimbabwean Demographic Health Survey.						

Table 1: Peer reviewed PUBLICATIONS both reviews and original RESEARCH, thematic area of prevalence studies; hepatocellular carcinoma, Transmission, treatment, molecular epidemiology including knowledge attitude and practices around viral hepatitis.

Studies investigated HCC burden, diagnosis approaches, including risk factors. HCC was most prevalent in young adults' median 45 years with a median survival of just 2.5 months. The majority of these young patients had advanced stages of the disease at their first presentation [41,42]. Presenting HCC symptoms included abdominal pain and swelling, weight loss, hepatomegaly often tender and nodular [43]. A 1992 cross sectional study of 182 HCC hospitalised patients at Parirenyatwa Central Hospital and 100 controls observed blood alpha feto protein (AFP) tumour marker levels of >1000ng/mL in 64.5% of the HCC patients [44]. This 64.5% detection rate of AFP in the 1990s was up from the detection rates of 47% observed in the 1970s [45,46]. This improvement could have been due to increasing sensitivity and specificity of the diagnostic test kits used over the years. Negative AFP marker in suspicious cases necessitated the need for liver biopsies, and the hepatic focal nodular hyperplasia was associated with HCC [47,48].

Risk factors for HCC

Risk factors for HCC included HBV and/or HCV infection(s), aflatoxin B1 exposure, high alcohol consumption and iron overload, with metabolic dysfunction associated fatty liver disease slowly emerging as another important risk factor over the past few years [41]. HIV/HBV co-infection increased the risk of HCC development with the lowest survival rates [49]. Frequencies of HBsAg and anti-HCV antibodies sero-prevalence in HCC patients ranged from 40%-48% and 20%-24%, respectively [50,51]. HBV/HCV and HBV/HIV coinfections seropositivity were about 8% and ranged from 5-29%, respectively, disproportionately affecting adult black males [41,42,52]. Younger HCC patients had higher detection rates of HBsAg/HIV sero-positivity but lower frequencies of the presence of anti-HCV-antibodies, whilst the situation was quite the opposite in older HCC patients [42,53]. Negative HBsAg seropositivity associated with abnormal levels of liver function enzymes in HCC or cirrhosis patients has been attributed to high alcohol consumption [46,54].

A 1987 rural study detected >40pg/ml of dietary exposures to aflatoxins in breast milk in 11% of lactating women with primary HCC compared to 0% in French controls (55). It is yet to be explored whether high levels of aflatoxins in breast milk are a risk a factor for the development of HCC in infants.

Viral hepatitis burden trends and situation

Of the forty-nine (49) original articles that met the inclusion criterion, twenty-two (44.9%) researched on viral hepatitis mono- and coinfections burden in rural, peri-urban, urban and

hospital settings. Population groups studied included the general population, pregnant/lactating women, infants/children, NRBDs, health professionals, PPnTSRs, outpatients and hospitalised patients. The HBV prevalence fell from >40% before the 1990s to ~3% around year 2022 with the burden remaining relatively high in the HIV-infected and PPnTSRs; Table 1. Five studies (10.2%), investigated the efficacy of different antiviral regimens in HBV/HCV-mono and –coinfection(s). HBV molecular epidemiological studies constituted 6.1% of the articles. There was paucity of data on occult HBV infection. Viral hepatitis molecular diagnostic facilities were non-existent.

Sound policies/acts, comprehensive health professionals' curricula, infant HBV vaccination, ensuring the safety of blood and blood products supplies, injection and sharp safety in both the conventional and traditional healthcare settings including beauty salons may have attributed to the reduced risks of both HCV and HBV infections acquisition as will be described in detail later on.

Acute viral hepatitis infection

A couple of studies on burden of acute viral hepatitis in were identified. A 1984 cross sectional survey observed a 61% anti-HBs and a 31.2% HAV antibody seropositivity in patients with acute viral hepatitis admitted at an Infectious Diseases Hospital in Harare [56]. The other study was a 1988 cross-sectional survey of hospitalised patients with acute HBV done at Parirenyatwa and Harare Central hospitals that reported a 16.2% HDV antibody seropositivity [57]. In patients with acute viral hepatitis, HBeAg and anti-HBc seropositivity rates were 49.2% and 89.2%, respectively [58]. There was a dearth of information on HEV. Since the 1980s, there has been no other published work on oral–faecal viral hepatitis despite decades' long challenges of water and sanitation particularly in the cities.

HBV and HCV burden in the general population

A 1990 systematic review and meta-analysis with PRISMA bias risk assessment standards reported an overall pooled HBsAg seroprevalence rates of 5-20% for SSA [59,60]. HBsAg seropositivity of 11% was reported in the general Zimbabwean population in the 2015 according to a WHO report, down from seroprevalence rates of 16.8% and 14.3% reported in the mid-1980s in rural and urban settings, respectively [61].

No HCV-antibodies were detected in the rural general population in 2003 [62]. Thus, ccontemporary data on both HBV and HCV in the general population is lacking.

HBV/HIV coinfection burden and trends

SSA is endemic for both HBV and HIV infections [61,63]. HBV/HIV co-infection has been associated with more rapid immune deterioration [33]. The Zimbabwean HIV Strategic Plan 2018–2020 mentioned the need for viral hepatitis screening in people living with HIV and AIDS (PLWHA). However, this is not being done, but only performed for symptomatic patients in public institutions. A SSA systematic review and meta-analysis that included Zimbabwean data covering the period 2004-2019 reported an overall pooled HBV/HIV coinfection rate of 3.3% with the years 2004-2010 recording higher prevalence rates of ~6.3% [52]. A 2017-2019 cross sectional study that analysed data routinely collected in urban PLWHA initiating antiretroviral therapy (ART), observed a 7.7%-12% HBsAg seropositivity that was associated with anaemia and elevated ALT levels [64,65]. Unusual HBV serology patterns were observed in 14% of HIV infected but immunosuppressed adults initiating Tenofovir (TDF) and Lamivudine (3TC) as part of combination ART between 2003 and 2009 [66]. Among the HBeAg seropositive ART naïve PLWHA with advanced disease, 79% had detectable HBV DNA. Some HBsAg-negative individuals were positive for anti-HBc IgG but without anti-HBs. Authors hypothesised that the isolated anti-HBc seropositive profile may be due to comorbities such as HIV infection and/or malnutrition. This observation warrants further investigations to better understand the impact of host immunosuppression in a setting where malnutrition is also common for the improved management of such patients. Combining HBsAg serology and HBV DNA assays is rarely done in Zimbabwe, yet studies have shown that combining these tests increases the prevalence of HBV from 4.8% (HBsAg alone) to 12.4% [67,68].

A 1978 cross sectional survey on HBsAg seroprevalence at a rural hospital in outpatients department recorded a lower HIV coinfection rate of 1.1% [69].

The HCV coinfection rate was 0.9% in HIV infected ART naïve adults presenting at Parirenyatwa Central Hospital's Opportunistic Infection Clinic in 2012, [70].

Blood safety and HBV burden

Up to 70% the total road network is in poor condition according to the 2017 Zimbabwe Road Condition and Inventory report, and casualties on the roads remain a challenge. Victims of road traffic accidents, including pregnant mothers during delivery are at risk of losing a lot of blood, and hence are at risk of acquiring HBV through blood and blood products during transfusion. The National Blood Transfusion Services (NBTS) is committed to the safety of blood and blood products that are free from transfusion transmissible infections (TTIs) through use of appropriate equipment and technologies [71]. Established since 1985 NBTS uses highly sensitive test for screening and highly specific confirmatory tests. The Abbott Architect i2000SR serology platform has been first line, and further testing done using rapid immunoassays. Additional ultra-sensitive nucleic acid

amplification testing and pathogen reduction technology are also available. However, these further increase the cost of blood and blood products [72,73]. TTIs screened include HBV, HCV, HIV and syphilis. The 2020 NBTS reported an HBsAg seroprevalence of <0.2% in NRBDs [74]. According to the earlier NBTS 2018 annual report, HBsAg sero-prevalence of 0.3%, and the anti-HCV detection rate of 0.005% were described [75]. These low figures were sharp declines compared to the >45% HBV seroprevalence reported in this population in 1988 [76]. The virus was by then of sub-genotype A1 [77].

Two studies investigated the cost effectiveness and estimated the residual transfusion of HBV in NRBDs. The HBV nucleic acid based and the serologic tests lowered the risks of HBV, HCV, and HIV transmission to 46.9, 0.3, and 2.7 per 100,000 donations, respectively [78]. In addition, the impact of using different models to estimate the transfusion transmission residual risk of HIV, HBV and HCV was done. One of the 3 models evaluated was the Schreiber incidence window period estimation of residual risk, and the results observed were comparable to the published related methods [79].

Timely and effective interventions over the years may have reversed the early alarming prevalence rates. These included employing more sensitive screening methods with the aim to close the HBV incidence window period by lowering the residual risk of HBV transmission through safe life-saving blood transfusions [78,79]. Test performance of rapid test to detect HCV antibodies in serum versus whole blood matrix showed a concordance of 97.6% [80]. Thus, the general population sexual behaviour change coupled with effective research and development strategies has seen TTIs decline, especially for HBV from as high as 40% in the 1980s to the current <2% [74].

HBV burden in sexual minority groups

In 2018-2019 the Columbia University's International Centre for AIDS care and Treatment Program (ICAP) in partnership with MoHCC and US Centres for Diseases Control and Prevention (CDC) with support from Gays and Lesbians of Zimbabwe (GALZ) implemented a formative assessment and bio-behavioural survey in PPnTSRs, including men who have sex with men, and transgender women/genderqueer individuals in the two main cities to better inform HIV prevention and control programs. In this hard to reach sexual minority groups the prevalence of active HBV infection was 3.3% and 4.3% in Harare and Bulawayo, respectively [81].

In GALZ living with HIV/AIDS, the HBV coinfection rate was 7.4% in Harare with the frequency being higher at 11.5% in Bulawayo [81]. PPnTSRs face societal harassment, violence and stigmatisation such that sexually transmitted infections spread easily as they shy away to seek medical care and preventive control strategies as the Zimbabwean Criminal Law Act 2006 criminalises homosexuality. Ensuring more equity and inclusivity in risk reduction packages for PPnTSR to reduce stigma, discrimination and criminalisation remains critical, more so with the current upward trends in use of illicit drugs/substances and alcohol abuse among adolescents and youths.

HBV burden in health professionals

There were two (4.1%) qualitative studies on knowledge, attitude and practices around HBV infection among private and public dental practitioners in Harare. One was done in 2006 and the other in 2013. Results showed that knowledge on the risk of HBV transmission was generally well appreciated. However, the uptake of HBV vaccination was low, with the 2006 study reporting that 91.7% of the hospital workers were not vaccinated against HBV [82,83]. The 1988 study reported an HBsAg sero-positivity rate of up to 58%, disproportionately affecting black health professional [82,83]. No other studies on HBV biomarkers have been done in this population since then despite the potential risk of contracting the infection.

Healthy workers and medical students are expected or encouraged to be vaccinated although the relatively younger ones are more likely to be vaccinated in childhood. There is no national HBV vaccination policy for risky groups such as health workers, medical students or pregnant women in both the private and public Institutions in Zimbabwe.

Ensuring injection/sharps safety

Needle stick injuries are a serious concern for health workers as they pose a significant risk of occupational transmission of blood borne pathogens including HBV, HCV and HIV. The most common unsafe injection practices include, unnecessary prescription of injections when oral alternatives are available, reuse of injection equipment, accidental needle-stick injuries and unsafe handling of sharps that have caused 21 million HBV infections (30% of new cases) globally [84,85] of which 90% were from Africa. The risk of acquiring HBV from an occupational needle stick injury when the source is HBsAg positive ranges from 2% to 40%, depending on the source's level of viremia [86]. Studies have shown that HBV can survive for up to one week under optimal conditions, and has been detected in discarded needles [87,88]. A statutory instrument on sharps waste management or the local Occupational Health & Safety Act; the Health Care and the Needle Safety Regulation is in place in line with the WHO injection safety policy [89] (Table 2). This policy abolished the reuse of needles in all healthcare settings with the aim to minimize the risks of needle stick injuries and environmental contamination to health care workers, patients and communities. Despite these noble policies in place, Harare city health recorded an increase in needle stick injuries among nurses from 1% in 2013 to 7% in 2016, and reasons for injuries included

limited space in the treatment rooms [90]. The burden of nationwide needle stick injuries are yet to be well described.

Timing of data collection/enacting	Setting and design/type of document	Population	Main focus of the documents/guidelines and Reference
Current - 2022	Curricula	Health Professions (Nurses (diploma and degreed), Doctors, pharmacists, lab scientists etc)	All taught according to WHO guidelines. 1. WHO guidelines/manual on hep B treatment [174] 2. Manual for the development of national viral hepatitis plans [175] 3. Global health sector strategy on viral hepatitis [176] 4. Management according to CDC [177].
2019-2022	Strategic plan	General Population	Strategic Plan for the Control and Elimination of Viral Hepatitis in Zimbabwe 2019-2022. Harare Zimbabwe: Ministry of Health and Child Care (MoHCC), Zimbabwe; 2019.
2016–2021	Strategic plan	General Population	The strategy calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%). The strategy covers the first six years of the post- 2015 health agenda, 2016–2021, building on the Prevention and Control of Viral Hepatitis Infection. Good progress in keeping the blood supply safe and improving injection safety in health-care settings which substantially reduces the risk of hepatitis C virus infections. [178]
2018	Public Health Act [Chapter 15:171, - No. ll/2018	General Population	Provides for the conditions for improvement of *the health* and quality of life and *the health* care. Stipulates that viral hepatitis in general is a notifiable communicable disease in Zimbabwe Implementing text Public Health (Standards for Personal Protective Apparel, Materials and Equipment) Regulations, 2020 (SI No. 92 of 2020). [179]
2017	Assessment	General Population	Viral Hepatitis Rapid Assessment Report 2017. Harare Zimbabwe: MoHCC.
2021	Essential Medicines List and Standard Treatment Guidelines for *Zimbabwe* (*EDLIZ*), 7th Edition and the essential Medicine List for Zimbabwe (EMLIZ)	General Population	Hepatitis B and C treatment has now been included EDLIZ MoHCC 2020 [180]
2021-2025	Pharmaceutical Manufacturing Strategy	General population	To boost local medicines production and lower the cost
2016	Zimbabwe National Health Financing Policy	General Population	Resourcing Pathway to Universal Health Coverage 2016.
2013	Zimbabwe National Infection Prevention and Control Guidelines 2013	General Population	Emphasizes infection prevention for staff and patients at all national health centres, [181]
2009-2013	The National Health Strategy	General Population	National Health Strategy

2005 to date	National Cancer Registry Zimbabwe	General population	Mentions liver cancer No statistics on HBV in specifically for pregnant women and their infants [182]
2020 – 2023	Strategic Plan for The Control and Elimination of Viral Hepatitis In Zimbabwe 2020 – 2023	General Population	Mention Zimbabwe's efforts Working Towards Elimination Of Viral Hepatitis As A Public Health Problem In Zimbabwe;MoHCC.
2015	Zimbabwe 2015 Demographic and Health Survey	General population	Mentions the mandatory three doses of HBV vaccinations during the 1st year of life, under childhood vaccination section
2013	Government of Zimbabwe. The Constitution of Zimbabwe Amendment. (No. 20) Act, 2013. Harare Zimbabwe: Government of Zimbabwe.	General population	Basic principles and laws determining powers and duties of government guaranteeing citizens' rights and obligation
2006	Section 73 of the Criminal Law Act 2006	General population	criminalises all sexual acts between men with a maximum penalty of one year imprisonment and the possibility of a fine this may negatively affect HBV prevention and management strategies [96].
1996	The patients' charter		Provides the framework on how patients should be treated and defines the responsibilities of patients within the health system to attain the best health care possible
The desk review identified 23 key standard viral hepatitis related documents; including acts/policies, guidelines, strategic plans or technical reports, an essential drug (medicine) list for the most common health conditions in Zimbabwe (EDLIZ) the Zimbabwean Constitution, ZNCR, health professionals' curricula for nurses, medical doctors, laboratory scientists and pharmacists including local newspapers report. **Abbreviation:** AFP: alpha-feto protein, HCC: Hepatocellular carcinoma, MoHCC: Ministry of Health and Child Care, ZDHS: Zimbabwean Demographic Health Survey, ZNCR: Zimbabwe National Cancer Registry			

Table 2: Policy Documents, Guidelines, strategic plans and Curricula on Hepatitis Infections [13]

Intravenous drug abuse and risk to HBV/HCV/HIV infection

The prevailing economic hardship characterised by high unemployment rates has resulted in a dramatic increase in young people both in rural and urban areas, who should be economically productive, becoming addictive to alcohol and illicit drugs with serious mental health consequences. Potent drugs include "guka" (cocaine), "mutoriro" (methamphetamine). Some of these abused drugs are administered intravenously using the same needle between different individuals, predisposing abusers to TTIs, including HBV and HCV. Even more concerning has been the so called "blue toothing" practice whereby the already drugged individual draws up their own blood with a syringe and injects their substance saturated blood to their craving addicts without the means to make them high too.

Evidence shows that intravenous drug abuse is on the increase especially among adolescents and youths [91]. It is estimated that 50% of reported mental health cases were due to disorders related to abuse of alcohol, use of stimulants like crystal methamphetamine [92]. The actual number of drug/substance abusers is still to be determined. The extent and contribution of these practices to HBV/HCV transmission remains poorly described.

This pandemic is unfolding at the time the country has shortages of clinical psychologists, psychiatrist including mental health nurses. Consequently, there has been an increase in mental health issues, a situation compounded by inadequate mental health rehabilitation facilities as well despite being provided for in the Mental Health Act Chapter 15:12.

HBV or HCV infection in Pregnant and lactating women

There were five HBV and one HCV prevalence studies done in pregnant women between 1985 and 2019. Two were rural based studies done prior to the ART era and these reported HBV monoinfection prevalence rates of 2-3.3% [93,94]. Interestingly, also done before the lifelong ART era, the investigation of the prevalence of HBV co-infection with Group B streptococcus which was 0.5% in rural pregnant women [95]. The prevalence of HBsAg coinfection with either *S. haematobium* or *S. mansoni* was 13% among rural pregnant women seeking antenatal services at a local primary health care clinic in 1995 [96]. HBV/HIV coinfection in pregnancy during the same period in the same setting was 0.8% [93].

A cross sectional survey of a random sample of 1000 urban women delivering at Harare Maternity Hospital in 1997 reported the frequency of HBsAg seropositivity of up to 25% [97].

The most recent paper recruited 1208 pregnant women ≥20 weeks' gestational age seeking antenatal care services from Harare municipal primary health centres in south western high density suburbs. In this study the overall, regardless of maternal HIV status, HBsAg sero-prevalence was 2.65%. The burden was almost four times higher in the 608 HIV-infected women 4.11% against 1.17% in their 600 HIV-uninfected peers [98]. The drastic decline of HBsAg prevalence rates observed from >25% in urban pregnant women before the ART era in the 1990s to the current overall 2.7% during this era of lifelong ART around 2019 is remarkable. This is probably partly due to the positive impact of lifelong ART usage for HIV control.

Interestingly, a 1999 study also done before the ART era observed an HCV antibody seropositivity of 1.6% in 1607 women delivering at a Harare Central hospital [99]. Contemporary data on HCV in pregnancy are yet to be described, and so are maternal HBV/HCV coinfection rates. Maternal HBV and HCV infections are the major route for vertical transmission and subsequent infant chronic infectivity [100]. Studies have shown that approximately 20% to 60% of children aged 1 to 5 years, and just 5% to 10% of older children including adults become chronically infected [101,102]. Untreated chronic HBV infection is associated with a 15% to 40% increased risk of the development of liver diseases [103].

Control measures; HBV screening in pregnant women

Ordinarily, all pregnant women should be universally screened for HBV, which is defined as testing positive for HBsAg, HBeAg, or both during the routine antenatal serological screening performed on an early antenatal visit as recommended [104]. Despite clear policies and guidelines in place, routine antenatal screening in public health institutions is limited due to resource constraints. Interestingly, back then in the 1990s in a Harare study authors cited the scarcity of financial resources as the reason of failure to routinely test all pregnant women for HBsAg in public health institutions [97]. Worryingly, the same financial challenge still stands today. In private institutions, it is standard practice to screen both expecting parents for HBV infection where serology laboratory facilities for HBV testing are more readily available but more expensive. However, in private practice antenatal HBV screening is not always guaranteed.

There is varying capacity to carry out laboratory tests from HBV serological, rapid diagnostic tests or molecular test that include viral loads, drug resistance and genotyping in the country at all levels of the health system. HBV molecular epidemiological and qualitative studies on knowledge attitude practices constituted 6.1% and 4.1% of the articles, respectively. The SD Bioline (Standard Diagnostics Inc., Kyonggi-do, South Korea) HBsAg test kit has been WHO evaluated locally and approved by the MoHCC for diagnostic use in Zimbabwe. There is no standardised testing algorithm for HBV infection.

Barriers in controlling viral hepatitis have included huge variation in the cost for serological tests which were about 22 times more expensive in private compared to public health facilities. The costs of viral hepatitis serology test ranged from US$0.60 to US$13 per test. Cheaper test kits are available in public health facilities but more often are in short supply leaving patients with no choice but to seek these services in private facilities where costs are exorbitant [105]. In the meeting with stakeholder, it was highlighted that molecular detection of HBV DNA load testing is non-existent in both the private and public sectors. Samples were shipped to South Africa for HBV viral load determination. Diagnostic inadequacies, uncoordinated, fragmented services and reporting may lead to significant underestimation of HBV infection in both public and private clinical settings. Routine antenatal HBV screening remains critical as it allows early identification of neonates who require HBV passive immunoprophylaxis at birth to reduce the risk of perinatal HBV transmission, especially in high-risk HBV/HIV co-infected pregnant women**.**

Immunisation of pregnant women

HBV vaccine is recommended for anyone at increased risk of contracting the infection, including pregnant women, and it is safe [106]. Pregnant women who test negative for HBsAg, but are at increased risk of acquiring HBV infection, should be immunised during pregnancy regardless of whether they are immune to HBV or not. Women considered to be at risk include those with multiple sexual partners (more than two in the last 6 months); those with a current or past history of sexually transmitted infections; recent or current intravenous drug users; including those with HBsAg-seropositive sexual partners [107].

Antenatal HBV infection and pregnancy outcomes

The presence of maternal HBeAg has been associated with increased risk of adverse pregnancy outcomes [108]. High maternal HBV DNA load was associated with HIV perinatal transmission [109]. During the intrapartum single dose Nevirapine era, HIV/HBV coinfection had no impact on infant mortality or maternal outcomes at 18 months follow up. However, high HBV DNA loads increased the risk of low birth weight, and potentially HIV perinatal transmission [109]. HBV-exposed-babies tended to be born prematurely [98]. In Asia, perinatal HBV transmission is the major route of childhood infection, whereas it is thought that transmission in Africa occurs predominantly in childhood through the horizontal route [110-112]. The exact mechanism by which postpartum transmission occurs remains unclear. Understanding these HBV transmission dynamics, including implementing the new classification of chronicity [113], and assessing the risk factors and biomarkers of susceptibility in this population is critical, more so because HBV infected pregnant women constitute a significant reservoir for both perinatal and horizontal HBV transmission. Pregnant women are yet to be universally tested for HBV to facilitate administration of hepatitis B immune globulin shortly after birth of exposed neonates. Preventive interventions targeting infants are critical since HBV infection acquired later in adulthood causes chronic hepatitis in only <5% of cases, whereas infection in infancy and/or early childhood leads to chronic hepatitis in 95% of cases [114,115].

HBV vaccination in infancy

Infancy vaccination strategy including timely administration of hepatitis B immunoglobulin to exposed new-borns have been recommended to eliminate HBV infections [115]. WHO recommends that all infants receive an initial dose of HBV vaccine within 24 hours of birth (birth dose), followed by subsequent 2 doses at least 4 weeks apart to complete the vaccination series [115]. HBV immunoprophylaxis has been shown to be effective in reducing both the incidence and mortality of hepatocellular cancer. HBV vaccine induces protective immunity in 90-*95*% of vaccinees [116,117].

Universal HBV infant immunisation as a monovalent vaccine at six weeks of age was instituted in Zimbabwe in 1988 followed by universal access since1996. The HBV vaccine is combined with other antigens in the form of Pentavalent. According to the Expanded Program on Immunisation (EPI) policy the Pentavalent should be administered at 6, 10 and 14 weeks of age. Pentavalent include HBV, diphtheria, tetanus, pertussis, and Haemophilus influenzae antigen preparations. An independent body of experts, from a diverse background, including Gynaecologist, Paediatricians, Immunologists, Epidemiologist and Health Economist with the mandate to guide, coordinate, make informed decisions on the vaccination program in line with WHO guidelines, the National Immunisation Technical Advisory Group (ZIMNITAG) was formed in 2017. Zimbabwe has achieved outstanding vaccination with the coverage of the first dose being 90%, and 83% children receiving their third dose of the Pentavalent that includes HBV vaccine [63]. This may have effectively arrested new infections in infants as shown in the dramatic decline of the disease as demonstrated by a recent study where none of the HBV-exposed-infants were HBsAg-seropositive by 2 years of age (98). Since universal HBV vaccination was instituted in 1988, it means a good proportion of the pregnant women were vaccinated in infancy and hence should test positive for anti-HBs. However, whether these maternal antibody titres are protective enough in adulthood, anti-HBs levels >10 mIU/mL) threshold [118,119] is yet to be ascertained.

A 2015 review paper on hepatitis B birth dose vaccine status in 47 African countries reported its presence in 11/47 nations [120]. However, this birth dose strategy has not yet been introduced in Zimbabwe in 2019. Resources to roll it out remain a challenge. Due

to the heath sector underfunding, administration of HBV vaccine at age 6 weeks rather than at birth remains a concern. The current administration of first dose of the HBV vaccine at 6 weeks of age rather than at birth remains a great concern as infants are thought to be vulnerable from birth until about 6 weeks, yet there is not much evidence on the burden of perinatal transmission of HBV. However, plans are underway for the introduction of this birth dose. The high proportion, 77%, of births occurring within health care facilities complemented by 8 in 10 deliveries assisted by skilled health provider [63] would facilitate a successful HBV birth dose implementation, in the process closing the window of HBV infection vulnerability in infants before 6 weeks of age particularly for those infants born of HBeAg and HBsAg seropositive mothers. The 20% home delivery rate at national level in 2015 [63] may have increased with the current harsh economic climate. This situation may be a challenge for the implementation of HBV birth dose vaccination. Follow-up strategy of HBV exposed infants for treatment including immunoglobulin passive therapy are not routinely done. Despite immunisation program being the effective, simple, and cost/effective public health intervention, there exist unreachable but vulnerable infants of a particular Apostolic sect who do not believe in seeking conventional medical help including vaccination. This may be contributing to a higher proportion of ~10% of children between 1-2 years of age who had never received any vaccination at any time before the 2015 ZDHS [63]. This is of great concern since herd immunity may be compromised. The COVID 19 lockdowns may have also impacted negatively on the immunisation coverage in general as recently witnessed by the re-emergence of measles outbreak that has taken a toll in these vulnerable unvaccinated children [121]. Worrying are polio virus cases on the rise in neighbouring Malawi and Mozambique [122]. HBV outbreaks may occur should many children refuse vaccination.

Vaccination in maternal HBV exposed infants

Despite successful HBV vaccinations, studies have shown that a significant number of HBsAg-negative infants, especially those born to HBeAg-positive mothers with HBV-DNA>6 $\log_{10}$ copies/mL are not immune to HBV [118,119]. The presence of anti-HBs is the only serological marker in individuals with HBV acquired immunity through vaccination distinguished by concurrence with anti-HBc IgG in cases of past natural HBV infections. No HBs-antibodies were detected at 2 years of age in 23.3% of HBsAg-exposed infants, despite having completed Hep B vaccination schedule, receiving the first dose at 6 weeks of age rather than at birth [98]. These children may have to be revaccinated with a second three dose series followed by retesting 1 to 2 months after the final dose. Host genetic variants play a role in hypo-immune responses to HBV vaccine and infection [123-125]. There are no local data on immunoprophylaxis failure rates nor the associated risk factors despite HBV infant immunisation being instituted in Zimbabwe over 30 years ago. Furthermore, there are gaps in immunoprophylaxis-failure rates in fully vaccinated maternally HBV-exposed babies. Other findings suggest that preterm infants, obesity and gender differences, type I diabetes mellitus, Down's syndrome and other forms of mental retardation and HIV infection may affect responses to HBV vaccines [126-128]. It also remains questionable whether the vaccination schedule should be the same between infants born of HIV infected and uninfected mothers.

Vaccination in HIV exposed infants

The vaccination policy and schedules are the same regardless whether the infants are born of HIV infected mothers; (HIV exposed and uninfected (HEU), HIV exposed and infected (HEI) or HIV unexposed uninfected (HUU) babies. As transplacental transfer of maternal antibodies may be significantly impaired in HIV-infected women, and HIV-exposed infants may receive lower titres of antibodies to HBsAg. The impact of this reduced placental antibody transfer following maternal HBV vaccination in infancy outcomes has not been determined. It is plausible that maternal antibodies transferred to the infant across the placenta may interfere with the efficacy of infant vaccination, as has been well-described for measles antibodies following infant measles vaccination [129]. However, human studies for HBV have shown inconsistent results [130,131]. Furthermore, whilst peak antibody responses to infant vaccines in HEU infants may be similar to HUU infants [132], several studies have reported impaired cellular responses to infant vaccines in HEU children [133] which could reduce antibody longevity. Evidence based policies are warranted as there may be need for an alternative vaccination schedule if immunoprophylaxis failure or reduced primary vaccination is confirmed to improve the health outcomes of the viruses exposed infants.

Five studies (10.2%) investigated HBV transmission between 2007 and 2019 and the oldest one in the late 1990s assessed the presence of maternal HBeAg. Authors postulated that these women were at high risk of transmitting HBV to their new-borns [134]. Their assumption was consistent with other previous findings that have shown that pregnant women with serological evidence of both HBsAg and HBeAg have a significantly greater risk of HBV mother to child transmission (MTCT) compared to women seropositive for HBsAg only, (85% versus 10%) [135]. 0.8% of the 1000 Harare pregnant women fell in this high risky category. Zimbabwean perinatal transmission rates have been <1% ever since the 1990s [98,136]. A recent local study showed absence of congenital HBV despite implementing the first dose at 6 weeks of age [98]. This conclusion may not necessarily represent the natural results of transmission due to lifelong Tenofovir/Lamivudine/Efavirenz exposures for HIV therapy since 78.1% of the HBV seropositive women were also coinfected with HIV and

were on ART based regimens that also interrupt HBV replication [98]. Lack of maternal anti-HBe antibodies also predicts HBV-MTCT [137]. Interestingly, during the lifelong ART era up to 47.9% of pregnant women tested positive for anti-HBe-antibodies compared to 3.3% in the pre-ART era [98].

HBV diagnosis in infants

Clinical diagnosis would include presence of jaundice. Ordinarily, presence of HBsAg and/or serum HBV-DNA in neonates is the criteria for determining intrauterine infection [138]. Venous blood from new-borns is recommended as opposed to cord blood samples in which contamination from maternal blood may result in false positive results. However, other studies have reported that this was insufficient evidence [139].

After completion of the vaccine series, testing for HBsAg and the antibody against HBsAg should be performed at 7 to 14 months of age [140]. Recent infants' follow up studies have shown loss of HBV markers; HBsAg, HBeAg and HBV-DNA at a frequency of 88%, 89% and 64%, respectively by the age of 8–12 months [119]. Thus, perinatal HBV diagnosis remains a challenge as even more sensitive and reliable diagnostic platforms have shown that in some cases neonates born of HBV infected pregnant women test HBsAg positive at birth but with absence of infection simply because the small molecular HBsAg passes through the placenta. In addition, anti-HBe and anti-HBc also cross the placental barrier in nearly all babies before disappearing in 12 and 24 months, respectively [141,142]. Again, these are just transplacental maternal antibodies transfers, but not indicators of infant HBV infection status. Hence detection of HBsAg, HBeAg, and HBV-DNA once at birth neither confirms nor excludes HBV-MTCT [119,143].

Lack of adequate molecular diagnostic facilities in many African centres may mean that vertical transmission is underappreciated. It is plausible that African infants are indeed infected with HBV at birth but due to poor diagnostic methods including differential host and viral genetic determinants, they persistently test negative until the virus is reactivated later in childhood. Despite the reported high prevalence of HIV in the general population of Zimbabwe, the rate of HIV/HBV co-infection amongst infants and children remains poorly reported.

HBV Treatment

The more sensitive, accurate and cheaper diagnostic laboratory tests coupled with highly potent direct acting antivirals with high cure rates have revolutionised the treatment of chronic viral hepatitis. The mainstay therapies for HBV infections are the oral antiretroviral nucleoside or nucleotide analogues which work by reducing viral replication. Tenofovir is an adenosine nucleotide analog approved for HIV treatment but owing to its poor bioavailability is usually available as Tenofovir disoproxil fumarate (TDF). Lamivudine (3TC), a dideoxynucleoside cytosine analog has antiviral effect against both HIV and HBV with 3TC based ART regimens achieving 30-60% HBV DNA suppression following 48 weeks of treatment. 3TC in combination with other antiviral agents such as Tenofovir Alfenamide (TAF) or TDF is an alternative option for HBV/HIV coinfected patients. Similar to 3TC, Emtricitabine (FTC) is a nucleoside with dual HBV/HIV antiviral effects. Thus, 3TC has been used far more extensively in pregnant women, but those with high viral load (>200 000 IU/ml) should be treated with TDF in the third trimester to minimize the risk of neonatal transmission according to the new EASL guidelines [27].

The EDLIZ 2020 edition that constitute the essential medicine list for the most common health conditions in Zimbabwe [144] has a section on the drug management of chronic HBV in adults; being TDF once daily for life for the HIV-uninfected. In the absence of this single formulation TDF and 3TC combination is recommended. During the stakeholders meeting it was highlighted that drugs for treatment of confirmed HBV; TDF and 3TC were readily available as combination therapy under the HIV treatment and care program, but single formulation/monotherapy for the HIV uninfected within the public sector were uncommon. It still remains unclear whether use of these HIV lifelong ART since 2013 has affected the general HBV epidemiological trends and trajectories. Once daily Sofosbuvir for 12 weeks is recommended for chronic HCV infections.

Between 2003 and 2016 there were four studies assessing the impact of ART regimens, 3TC alone as a monotherapy versus dual 3TC plus TDF and the primary end point was HBV DNA suppression below 200IU/mL [109,145], and perinatal outcomes [98,108,109]. 3TC monotherapy showed highly durable suppressive effect up until 5 years, in HBV/HIV coinfected adults with HBV DNA baseline levels of $<6\log_{10}$ IU/mL, but was associated with emergence of resistant mutants [146,147]. In treatment of multidrug resistant chronic HBV, the efficacy of TDF monotherapy has been shown not to differ from that of the TDF-based combination therapy [148]. TDF has been increasingly used for treatment of both HIV- and prevention of HBV-MTCT, and mother can safely breastfeed [149]. Other than 3TC and TDF, other antiviral agents for treatment of HBV infection like Telbivudine, Adefovir, Entecavir, and Emtricitabine are also safe in pregnancy [150]. Meta-analysis has shown Telbivudine to be more effective than 3TC for preventing vertical transmission of HBV infection [151,152].

Treatment Monitoring and end points

HBV management requires informed decision making in timing or discontinuing or switching antiviral therapy. It is

also crucial to timely distinguish or classify acute, chronic and occult cases of HBV to assess the clinical phases of infection for prognosis, initiation and monitoring of antiviral therapy. Treatment end points for functional cure or even clinical cure are HBeAg seroconversion, and preferably HBsAg seroconversion as this latter endpoint is associated with sustained immune control and the halting of disease progression [153,24]. Serial monitoring of HBeAg and anti-HBe are important to assess the phase of chronic HIV infection with serum HBV DNA, ALT measurements augmenting diagnosis, phase chronicity, decision to treat and subsequent monitoring as recommended in the 2017 EASL guidelines [24]. The end point of therapy of patients with chronic HBV infection negative for HBeAg is more difficult to determine than for HBeAg-positive patients because HBeAg seroconversion marker cannot be applied. The only useful markers of therapy efficiency are the suppression of HBV DNA replication and normalization of ALT levels [154]. No such longitudinal studies have been done locally. However, a couple of research studies done in the 2009 assessed reduction of HBV DNA levels especially below the detection limit and normalization of ALT values [155,156]. Serum HBV DNA levels≥2000 IU/mL has been associated with increased risk of developing HCC over time [157].

The robust and automated Roche system in place at the Sally Mugabe National Reference Microbiology Labs in Harare currently for testing HIV RNA load could also be used for HBV DNA quantification. There are no guidelines for HBV management algorithm in place. Zimbabwe is still to develop one or adopt management algorithms like the one by Yogeswaran and Fung [158]. Outside research no molecular HBV testing is being done even in the private labs. There is no national strategy for monitoring development of HBV resistance to antiviral treatment. Of concern were the non-existence of HBV/HCV diagnosis, treatment monitoring algorithms and end/points. No guidelines exist specifically for pregnant women for their treatment and mitigation of perinatal transmission.

The Basics

A strong foundation in teaching and learning

Knowledge is power, and as such viral hepatitis training is embedded in health professionals' curricula for nurses, medical doctors, laboratory scientists and pharmacists. It is part of continuing medical education for health personnel, with generally good attitudes and practices. Qualitative studies on knowledge-attitude-practices constituted 4.1% of the articles. Studies have shown that well trained health workers should give health education and counsel patients on potential risks that can predispose them to viral hepatitis [159]. Thus, there is a significant positive relationship between the knowledge and practice of pregnant women and health care workers knowledge on HBV prevention [160]. Despite being part of most life sciences degrees' curricula, most higher learning institutions' research agendas are silent on HBV as priority research area. In addition, the most recent ZHDS that assesses demography and health information every five years since 1988 is silent on HBV infection, except mentioning HBV vaccinations under childhood vaccination section [63]. This 5-year national survey assesses burden, knowledge and attitude of common infections, including of HIV, malaria, diarrhoeal diseases in a representative sample with a minimum of 11000 households nationwide [63].

Community Engagement and public awareness

There was a dearth of information on oral-faecal viral hepatitis, particularly hepatitis E virus. A 1984 study observed a hepatitis A virus sero-prevalence of 31.2% in hospitalised patients with acute HBV infection. In the stakeholder meeting it was noted that despite the presence of potential risk of oral-faecal transmission route due to unsafe water including poor sanitation and poor personal hygiene especially in urban areas where water and sewer infrastructures are overwhelmed, awareness is low.

In endemic areas, HBV is spread mainly from an infected mother to her child at birth or by the horizontal route through mastication of foods or traditional herbs, use of unsterile sharps or from an infected sibling to an uninfected child during the first 5 years of life [110]. The Rapid HBV assessment of 2017 has shown that, there is low viral hepatitis awareness among the general population; Table 2**.** Furthermore, commemoration of the World Hepatitis Day that falls on 28 July of each year is not well publicised compared to say HIV/AIDS day. Thus, there is need to intensify efforts of health care workers, especially midwives to educate expectant mothers on viral hepatitis in the antenatal care clinics during the education/counselling sessions.

In the stakeholders meeting it was noted with concern that unlike HIV/AIDS, gender based violence or cervical cancer awareness campaigns, there were no documented public awareness activities being carried out for Viral Hepatitis in Zimbabwe on the traditional and social media platforms. Thus, there is need to establish comprehensive HBV services at all health care levels including improving community HBV awareness and prevention strategies. This includes level of awareness on the existence of the disease in population groups that are at risk. Populace knowledge regarding HBV and HCV transmission modes was very limited. The population should be aware of the main modes of transmission.

Common practices and viral hepatitis transmission

Cultural practice of mastication of infant hard foods or medications

The common cultural practice of mastication of infant hard foods or medications by mothers "kuurira/ kutsengera mwana in venacular" is a potential source of HBV infection that must be discouraged during health education session of pregnant women.

Potential mechanisms of transmission involve close contact of the infant with HBV infected maternal secretions through kissing of the infant on the mouth; ingestion of masticated contaminated foods and nosocomial infection due to poor hand hygiene practices amongst healthcare workers who are involved in the postpartum care of both mothers and infants [161].

Home based use of sharps

In addition, some social cultural practices like home based ear piercing and tattooing of patients by traditional healers may impede or undermine the control of viral hepatitis. Traditional tattooing (kutemwa nyora in vernacular) or scarification in traditional medicine practice is a potential risk of parenteral transmission of HBV. Thus, it is critical that traditional healers be conscientised on the dangers of repeated use of the unsterilized instruments between and among different people or patients seeking their services. Hence continued community awareness and knowledge are warranted.

Conventional beauty treatments that use sharps

Common beauty treatments like ear-piercing, in the process of receiving the services of a manicurist and/or barber without access to sterilizing facilities can expose customers to HBV and HCV [162]. In poor settings prioritisation of cheaper services is common without being aware of the potential health hazard associated with equipment that is continuously used on many customers without being sterilised after being used on each customer. HBV is very infectious and can survive outside the body for up to 7 days, even on table tops, workbenches and other instruments, making it highly transmissible through contaminated razors and blades [163].

Local Authorities enforce and uphold by-laws that promote good hygiene and safety process as enshrined in the local Occupational Health & Safety Act. This Act empowers the Municipal police impromptu inspections of service providers' premises, arrests and or penalises any by-law breaches.

Use of sharps in Traditional medicine practice

To safeguard the health of the nation at large, Traditional healers are regulated under Zimbabwe's 1981 Traditional Medical Practitioners Act [27:14] that provides for the registration and regulation of the practice of traditional medical practitioners. Among other requirements this Act encourages single use of sharps [164].

Health financing

The main sources of health financing have been mainly external aid, voluntary health insurance contribution, out of pocket payment and government transfer at about 30%, 27%, 25% and 18%, respectively [165]. Out of pocket spending has pushed ordinary Zimbabweans into deeper poverty and relying on external aid is unsustainable, unpredictable and dwindled over the years. It is dependent on the political environment and subject to the external funders' interests and not necessarily the country priority health needs. Health financing has been negatively affected by the prevailing political, socio-economic challenges exacerbated by high inflationary environment initially between 2005 and 2008 and now since 2019 situations that greatly eroded the value of funds allocated to the health sector. Poor wages/salaries of employees lag behind and are not in keeping with prices of goods and services to facilitate a decent health service delivery. The prevailing economic decline and political instability have led to shrinkages in health care budgets over the years, negatively impacting access to the conventional health care system.

The Abuja Declaration of 2001 is a commitment by African heads of states to commit at least 15% of their annual budgets to fund the health sector. The annual budget allocation has been declining over the years and inconsistent with the Abuja declaration of which Zimbabwe is a signatory to, with MoHCC being allocated $474.7 billion Zimbabwean dollars (11.2%) against the national budget of 4,5 trillion in year 2023 [165]. Central and provincial Hospitals received a paltry 113 and $35 billion, respectively. This paltry funding incapacitates hospitals to neither deliver meaningful services nor curb massive brain drain. The country per capita (per person) spending on health dropped from US $45 in 2021 to just US$20 this year. There was a decline in health sector funds allocation from 13% in 2021 to 10.6% in 2022 a fall far short of the US$84 per year recommended by the WHO [166], a development inconsistent with the Abuja declaration. The issues of inadequate funding are not new. A 2006 study of Dental therapist reported that lack of barriers to infection control was attributed to non-availability of gloves and disinfectants [82] during screening of pregnant women in the 1990s. The current challenges of economic growth worsened by a turbulent global market means that this strategy cannot be business as usual as the country needs to find innovative ways of supporting the health sector.

To succeed in the 2016-2022 Health Development fund, the Minister of health launched a Health Resilient Fund and strategies to improve the provision of Health services to the nation [167]. There are currently challenges in the context of inadequate health financing, human resources for health, or poor health governance, health service delivery, health information systems including pharmaceutical management. Financial challenges are top on the list followed by uncoordinated planning on priority tasks and goals by stakeholders as controls and management of communicable diseases including HBV, are done in silos lacking the much needed holistic, cost effective horizontal integration approach.

Zimbabwe has a centralised health commodity nested at the National Pharmaceutical Company of Zimbabwe (NatPharm) and

is expected to be self-sustained through its reliance on registration fees and funding from Medicine Control Authority of Zimbabwe (MCAZ). However, the current economic climate handicapped the self-financing of NatPharm and MCAZ systems resulting in stock-outs of essential drugs and vaccines increasing propensity to rely on donor –supported vertical programs. Most pharmaceuticals and health commodities are provided donors through direct procurement and supplies for specific vertical programs like HIV/AIDS and malaria or provision of primary care kits to Nat Pharm. However, more often than not they are in short supply [105]. Encouragingly, the Government of Zimbabwe has since launched the 2021-2025 Pharmaceutical Strategy, which is meant to increase local drug production currently at 12%. Furthermore, this development is expected to improve availability and access of the country's essential drugs. More importantly this strategy seeks to remove middleman and enable the public health sector to buy drugs directly from the manufacturers, in the process reducing prices and inequalities.

Health Equity and inclusion

Adolescent girls and young women (AGYW) aged ≤ years are generally more vulnerable. Policy-makers should strive to reduce inequalities fuelling the HIV-epidemic, strengthen sustainable-livelihood-support for the vulnerable AGYW to diseases that disproportionately affect this group. Zimbabwe is one of the 67 countries or jurisdictions globally that criminalise consensual same sex activities. Same-sex sexual activities are prohibited under both the Zimbabwean culture and under the Criminal Law Act of 2006. The Act criminalises acts of sodomy or discriminates against PPnTSRs. Thus, homosexuality is a crime that carries a maximum penalty of up to one year of imprisonment [168,169]. Probably there is need to revisit the Criminal Law Act 2006 so as to reach this discriminated sexual minority group where HBV prevalence is much higher than the national average.

Surveillance and monitoring

Surveillance and monitoring information was mainly obtained from the stakeholders' meetings. The health information system is generally well structured and of high accuracy relative to other countries in the region. However, meeting the timelines may be a challenge due to skeleton staff manning the health centres as a result of the prevailing brain drain challenges. Computerization is very limited and/or internet connection is intermittent and costly.

Up to date and accurate epidemiological data on liver-related mortality are lacking. Verbal autopsy remains the main method of ascertaining the cause of death, and may underestimate the true burden of the disease. Unlike the successful on-going nationwide HIV sentinel sites, there is no systematic collection of data on HBV/HCV to ensure seamless and timely decision making and rapid critical information flow. A national estimate of HBsAg seropositive women of child bearing age would help public health programs plan surveillance, educational, and outreach activities to improve the identification and management of at-risk women and infants. There is a need to establish a national viral hepatitis surveillance system, particularly HBV to monitor the trends in incidence, and identify risk factors for new infections in the general population and this could be integrated into the on-going HIV one to avoid duplication of efforts. Existing capacity, infrastructure and service provision for the successful on-going HIV/syphilis prevention program framework could be adjusted to incorporate HBV/HCV prevention and care services. Human resources constraints and at times erratic supplies of fuel, the most expensive commodity in the region have compromised effective supervision and monitoring in the general health system.

Strength and limitation

The strength of this paper is the fact that all viral hepatitis studies done in Zimbabwe to date were included for a more comprehensive appreciation of the achievements, gaps and challenges over the past 50 years. In addition, information from the desk review and outcome of the stakeholders' meetings enriched our findings. However, due to the heterogeneity of the study designs, populations studied including the lab methods and/or test kits employed over different time lines, it was not possible to comprehensively compare and contrast the results.

Conclusion

The current evidence is suggestive of Zimbabwe being on course to meet the global targets aligned with the SDG 3 aiming to eradicate HBV epidemic by 2030, reduce new infections by 90% and mortality by 65%. There are clear policies, documents and instruments but inadequate practical actions to convert these excellent frameworks into efficient self-sustaining local practical solutions for more effective viral hepatitis control. Surveillance and monitoring systems are yet to be established and so are standardised management algorithms in both the public and private institutions. Policy-makers should strive to reduce inequalities fuelling the HBV-epidemic, especially supporting the sexually discriminated with the highest disease burden in the process promoting equality and diversity. Thus, ensuring an inclusive health-care to reduce and eliminate viral hepatitis burden is critical. There is need for a greater impetus to coordinate and optimise efforts of policy-makers, epidemiologists, clinicians, community advocacy groups, government and international research funders to improve strategies for prevention and management of viral hepatitis.

Declaration

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

The datasets obtained during this study will be available upon reasonable request to the corresponding author.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

The idea was conceived by KD designed by KD, FZG, RBLG, SB and TM. All authors, were responsible for data collection, overseen by KD. The manuscript was written by KD. All authors were involved in manuscript revisions and approved the final draft.

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