HIV AND HEPATITIS B/C CO-INFECTION IN KWAZULU-NATAL FROM 2002 TO 2010: A RETROSPECTIVE DATABASE ANALYSIS

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BY

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ABSTRACT

Introduction

Sub-Saharan Africa has the highest Human Immunodeficiency Virus (HIV) prevalence and the second highest Hepatitis B virus (HBV) and Hepatitis C virus (HCV) prevalence in the world. Co-infection of HIV, HBV and HCV occurs due to shared transmission routes and common risk factors.

Existing studies from sub-Saharan Africa show wide variations in the prevalence of co-infections, depending on age, gender, race and geographical area.

Aim

The aim of this study was to describe HIV and HBV/HCV co-infections in KwaZulu-Natal from 2002 to 2010 using a laboratory database.

Methods

An observational, analytical, retrospective study design was used. The study setting was the National Health Laboratory Service Department of Virology, in Durban. The study population consisted of 507 834 individuals (all those with HIV, HBV or HCV test results from 2002 to 2010 recorded in the database).

Results

The overall sero-prevalence of HIV was 47%, HBV:12.05% and HCV:4.13%. The highest sero-prevalence of HIV and HCV was in the 30-35 year age group; for HBV it was in the 20-25 year age group. HIV sero-prevalence was higher in females, while HBV and HCV sero-prevalence was higher in males.

The uThukela, Amajuba and Zululand health districts had the highest HIV, HBV and HCV sero-prevalence respectively. The sero-prevalence of HIV and HBV has decreased significantly over time, while there was no significant change in the sero-prevalence of HCV.

Compared to those without HIV, individuals with HIV had increased odds of being positive for hepatitis markers: 3.19 for Hepatitis B surface antigen, 2.06 for Hepatitis B e antigen and 2.91 for HCV. Those with HIV were less likely to be positive for Hepatitis B surface antibodies. Those with Hepatitis B had a 1.38 times the odds of being co-infected with HCV compared to those without HBV.

Discussion

This study documented the high sero-prevalence of HIV, HBV and HCV over 9 years for KwaZulu-Natal. A significant number of HIV positive individuals are co-infected with either HBV or HCV.

Recommendations

The results of this study may guide public health decisions on the approach to diagnosis, treatment and prevention of HBV and HCV among those with HIV.

DECLARATION

I, Nerisha Tathiah declare that:

i. The research reported in this dissertation, except where otherwise indicated, and is my original research.

ii. This dissertation has not been submitted for any degree or examination at any other university.

iii. This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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PUBLICATIONS OR PRESENTATIONS

Publication

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ACRONYMS AND ABBREVIATIONS

AIDS - Acquired Immunodeficiency Syndrome

ARVs - Antiretrovirals

ART - Antiretroviral Therapy

CI - Confidence Interval

ELISA - Enzyme-Linked Immunosorbent Assay

HBeAg - Hepatitis B e antigen

HBsAb - Hepatitis B surface antibody

HBsAg - Hepatitis B surface antigen

HIV - Human Immunodeficiency Virus

HBV - Hepatitis B Virus

HCV - Hepatitis C Virus

HIV - Human Immunodeficiency Virus

IgG - Immunoglobulin G

KZN - KwaZulu-Natal

LIS – Laboratory Information System

MTCT – Mother to Child Transmission

NHLS - National Health Laboratory Service

OR - Odds Ratio

PCR - Polymerase Chain Reaction

RR - Risk Ratio

SANAS - South African National Accreditation System

WHO - World Health Organization

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1 CHAPTER I: INTRODUCTION

1.1 INTRODUCTION

Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are important global public health problems. Sub-Saharan Africa has the highest HIV prevalence, as well as the second highest HBV and HCV prevalence in the world [1-3].

Co-infection of HIV, HBV and HCV is due to shared transmission routes and common risk factors. HIV affects the epidemiology and worsens disease progression in HBV and HCV co-infected individuals. The increased access to antiretroviral therapy (ART) has extended the life expectancy of those living with HIV. However, there is a greater potential for morbidity due to drug interactions and treatment side effects in those with co-infections [1, 4].

The majority of previous studies on HIV, HBV and HCV co-infections are from high income settings and focus on high risk groups. There are differences between mode and time of transmission between high and middle to low income countries. Existing studies from sub-Saharan Africa show a wide variation in the prevalence of co-infections, depending on age, gender, race and geographical area [5]. There is a paucity of population based data on the prevalence of HIV and HBV and HCV co-infections in South Africa.

1.2 BACKGROUND

1.2.1 HIV

Epidemiology

Over the past three decades, HIV has been responsible for more than 25 million deaths, worldwide [2]. In 2012, there were approximately 35.3 million (95% Confidence Interval (CI) 32.2-38.8 million) people living with HIV; of these more than 9.7 million people were receiving ART in low and middle income countries [2]. Furthermore, the burden of HIV has a disproportionate effect on sub-Saharan Africa; in 2012, 70% of all new HIV infections occurred in sub-Saharan countries [2].

South Africa has one of the fastest growing HIV epidemics in the world, and is currently the country with the highest number of people living with HIV [6]. According to 2011 estimates from the WHO/UNAIDS Reference Group, 5 600 000 people were living with HIV and AIDS in South Africa [7]; 270 000 South Africans died of AIDS-related causes, and 1.79 million (95% CI 1.65-1.93 million) people were on ART [8].

The rollout of ART in South Africa is associated with an 11.3 year gain in adult life expectancy. In 2003, prior to ART being available in the public health sector, adult life expectancy was 49.2 years; by 2011, adult life expectancy increased to 60.5 years [9].

A defining feature of the South African HIV epidemic is the burden of HIV infections in young women, with the additional implications for Mother to Child Transmission (MTCT). HIV infection is three to six times higher in female than male adolescents; this difference is due to sexual relationships between young women and older men. The high HIV prevalence, concurrent and total number of sexual relationships and other sexually transmitted diseases and population mobility further increase the probability of HIV infection in South Africa [10].

The HIV prevalence in South Africa varies by age, gender and geographic area [6]. Data from the 2011 National Antenatal Survey (used as a proxy indicator for monitoring the spread of HIV in the heterosexual population) indicated a stable HIV prevalence of 29.5% (95% CI 28.7%-30.2%), among pregnant women (aged 15-49 years) attending antenatal clinics in the public sector [11]. Nationally, there was a slight decrease in the HIV prevalence among the 15-19 year age group to 12.7% (95% CI 11.8%-13.6%) while HIV prevalence among the 30-34 year age group had increased to 42.2% (95% CI 40.6%-43.7%) [11].

The 2011 HIV prevalence in KwaZulu-Natal (KZN) was the highest in the country (37.4%, 95% CI 35.8%-39.0%), compared to Western Cape (18.2%, 95% CI 14.3%-22.8%). Within KZN, there was also variation between districts. uMzinyathi district had the lowest HIV prevalence 24.6 % (95% CI 20.4%-29.4%), with Ugu and uMkhanyakude districts each having a prevalence of over 40% [11].

Transmission

The transmission of HIV involves the direct transfer of genital, rectal or oral fluids through sexual intercourse, sharing of blood-contaminated needles, maternal (*in utero*, intrapartum, postpartum - breastfeeding), and medical procedures (e.g. transfusions or exposure to contaminated instruments) [12].

Factors that increase the risk of contracting HIV include: unprotected intercourse; sexually transmitted infections; contaminated injection equipment; blood transfusions, unsterile cutting or piercing; and accidental needle stick injuries among health care workers [12].

HIV has spread in two epidemiologically distinct patterns: (1) Men having sex with men (MSM) intercourse, or contact with infected blood (e.g. through sharing needles in injection drug users; and through transfusions, prior to the effective screening of donors), and (2) heterosexual intercourse. In most countries, both patterns occur, but the first pattern usually predominates in higher income countries; the second pattern predominates in sub-Saharan Africa, South America, and southern Asia [12].

The HIV epidemic in South Africa before 1987 was concentrated among MSM, and recipients of blood products [6]. Once HIV was introduced into the heterosexual population, prevalence increased exponentially (1995 to 2000) [6]. Since 2000, the rate of increase has slowed substantially, though there is still the continuing problem of large numbers of new HIV infections [6]. In 2001 South Africa implemented a MTCT programme to prevent HIV transmission from mother to child [13]. In 2012, the national MTCT of HIV was 3.5% (95% CI 2.9%-4.1%); for the same period the MTCT of HIV for KZN was 2.9 (95% CI 1.7%-4.0%) [13].

Clinical

HIV is a RNA retrovirus that targets CD4+ lymphocytes and impairs cell-mediated immunity. Manifestations range from asymptomatic carriage to AIDS (Acquired Immune Deficiency Syndrome), which is defined by serious opportunistic infections or a CD4 count of < 200 cells/µl. The widespread availability of life saving ART ensures an increased life expectancy in people living with HIV [12].

Laboratory diagnosis

There are two approaches to the diagnosis of HIV: the detection of the virus itself (HIV RNA or p24 antigen testing), and the detection of an immunological response to the virus, using ELISA (Enzyme-Linked Immunosorbent Assay) tests. False negatives may occur during the "window period" of 3 to 6 weeks during which antibodies to HIV are not yet detectable. Early diagnosis relies on the detection of viral antigen or HIV RNA. A diagnosis of MTCT uses nucleic acid testing, or antibodies in the case of infants >15 (or 18 months). Prevalence assessments are generally based on antibody testing [14].

Treatment

While there is no cure for HIV, the viral load can be suppressed below detectable limits by combination ART consisting of three or more antiretrovirals (ARVs) [6].

Prevention

Individuals can reduce the risk of HIV infection by the use of male and female condoms [15], voluntary medical male circumcision[16, 17], harm reduction for injecting drug users [15]; and the use of ARVs (either as pre-exposure oral prophylaxis in individuals engaging in risky behaviours [18], or as post-exposure prophylaxis in healthcare workers with needlestick injuries [19], or in MTCT [13]).

1.2.2. HBV

Epidemiology

Globally, 350 million people are chronically infected with HBV, of which 4 million are acute cases. One million people die per year due to the chronic consequences of HBV [1, 20].

Based on the prevalence of chronic HBV infection, the world is divided into three areas: Low endemic areas (<2% HBsAg prevalence), intermediate endemic areas (2-8% HBsAg prevalence) and high endemic areas (<8% p HBsAg prevalence) [1, 20].

Low endemic areas include North America, Western and Northern Europe, Australia, and parts of South America. Most infections occur in high risk populations (injection drug users, individuals with multiple sexual partners, and MSM) [1, 20].

High endemic areas include almost three quarters of the world's population - sub-Saharan Africa, Southeast Asia, Amazon Basin, Middle East, central Asian Republics and Eastern Europe. In Asia, mother to child spread is very common [1, 20]. In sub-Saharan Africa, especially in countries such as South Africa, Botswana, Zambia and Zimbabwe, HBV is most commonly spread by person to person contact in early childhood [21].

The introduction of the Hepatitis B vaccine into the Department of Health's Expanded Programme on Immunisation (EPI) in 1995 has changed the epidemiology of HBV in South Africa [22]. Prior to introduction of the Hepatitis B vaccine, 8-9% of children < 1 year of age were HBsAg positive [22, 23]. Subsequent studies on vaccinated children have shown a much lower prevalence (range 0.0%-2.7%) [22, 24-27].

South African HBV prevalence also differs based on age, gender, race and geographical location.

In a study conducted on rural and urban children in KZN, 2.5% of the newborn to six years age group was HBsAg positive. The prevalence of HBsAg was highest in the 6-8 year age group and was 14.4% and 22.6% in urban and rural children respectively [28]. In a subsequent study almost three quarters of the household contacts of infected children were found to have evidence of HBV infection [29]. A sero-prevalence survey conducted in 1999 of children in the Eastern Cape, reported a HBV prevalence of 10.4% with a higher prevalence (15.7%) in 5-6 year olds [23].

In adults, HBV prevalence ranged from 8.3% in women attending antenatal clinics, to 10% in mine workers [21]. Although both sexes were exposed to HBV, males were more likely to develop chronic HBV infection than females (male to female ratio of 2.6:1) [22, 30].

The prevalence of chronic HBV infection in black South Africans was estimated to range from 9.6% to 14%, with 76% having previous exposure to HBV [22, 31]. In contrast, the prevalence in Caucasians, and Indians was less than 1%, with 5% having previous exposure [22, 32].

HBV prevalence varied between rural and urban populations , with a prevalence of chronic HBV in the rural Eastern Cape of 15.5%, compared to urban areas such as Durban (7.4%) and Soweto (1.3%) [22, 32]. The prevalence of HBV varied in those without HIV: 10% in rural, and 1% in urban areas [33, 34].

There are few representative studies on HBV prevalence in South Africa.

Transmission

HBV is transmitted through contact with blood or other body fluids of an infected person. HBV is 100 times more infectious than HIV. There are multiple routes for the transmission of HBV (mother to child, horizontal, sexual, injection drug use and iatrogenic) [1, 20, 35].

Mother to child transmission occurs either *in utero*, during delivery or in the perinatal period, through the close contact between mother and baby [1, 20, 35]. In South Africa, while mother to child transmission does occur, it is not the major transmission route for HBV [22].

The major route of transmission in South Africa occurs between toddlers and is horizontal in nature (unrelated to sexual, perinatal, or parenteral exposure). Transmission may occur through ritual scarification, open wounds and saliva. An estimated 20-30% of those horizontally infected before age 5 proceed to chronicity. HBV infection during early childhood can lead to adolescents being infected by the time they are sexually active. Sexual transmission is the predominant mode of transmission in adolescence and early adulthood, with 3-5% of those infected progressing to chronicity [22].

Illicit injection drug use is an important route of transmission in low endemic areas. Iatrogenic transmission (through unsafe therapeutic injections and contaminated blood transfusions) are responsible for 21 million HBV infections each year, mostly in areas where HBV is highly endemic [1, 20, 35]. However, in South Africa, the risk is reduced due to the screening of blood donations by nucleic acid testing. Nonetheless, South African healthcare workers and patients are at high risk for acquiring HBV infection in healthcare settings [22].

Clinical

HBV is a hepatotropic virus that causes a wide spectrum of liver disease ranging from an asymptomatic infection to acute liver failure or chronic liver disease [20, 35].

HBV may be detected 30 to 60 days after infection and persists for variable periods of time. Symptoms of acute infection with HBV can last for weeks or persist for up to six months [20, 35].

More than 90% of healthy adults who are infected with HBV will completely clear the virus within six months and will recover. The remainder will develop chronic hepatitis or become inactive carriers. Cirrhosis can be a consequence of infection; hepatocellular carcinoma can develop in chronic HBV carriers, even without preceding cirrhosis [20, 35].

The possibility that HBV infection becomes chronic depends upon the age at which a person becomes infected. Children who are infected before they are 6 years old are the most likely to develop chronic infections: 80-90% of infants infected during the first year of life, and 30-50% of children infected before the age of 6 years will develop chronic infections. In adults, 15-25% of those who are chronically infected during childhood will die from complications related to HBV [20].

Chronic HBV infection is more likely to develop in those with congenital or acquired immunodeficiency (including HIV). Only those who develop antibodies following vaccination or infection are immune to HBV [20, 35].

Laboratory diagnosis

Laboratory diagnosis of HBV infection is based on the detection of the Hepatitis B surface antigen (HBsAg). Acute HBV infection is identified by HBsAg, immunoglobulin M (IgM) antibody to Hepatitis B core antigen (HBcAg) and Hepatitis B e antigen (HBeAg), which is an indicator of active viral replication and greater infectivity. The HBeAg marker is more useful in prognosis than in diagnosis. Chronic liver disease develops more often among patients with HBeAg [20, 35].

Chronic infection is defined by HBsAg persistence beyond 6 months. In 5 to 10% of patients, antibodies do not develop and HBsAg persists; these patients become asymptomatic carriers or develop chronic hepatitis. HBsAg persistence is the most important indicator for the development of chronic liver disease and hepatocellular carcinoma later in life. HBV-DNA is detectable by Polymerase Chain Reaction (PCR) in patients with active HBV infection [20, 35].

Surveillance

South Africa has a system for the routine reporting of notifiable medical conditions, including Hepatitis B and C. This is a passive surveillance system managed by the National Department of Health (NDOH) [36]. A challenge with such a passive reporting system is the associated under diagnosis and under reporting [37, 38].

Treatment

Individuals with chronic HBV can be treated with antiviral agents. Treatment cannot completely eradicate HBV but can slow the development of complications (including cirrhosis and hepatocellular carcinoma) thereby improving long term survival. Treatment is not accessible or available in many resource-constrained settings [20, 35].

Prevention

General prevention measures

HBV transmission can be prevented by the implementation of quality assured blood safety strategies (including screening) and safe injection practices. Safer sexual practices also protect against transmission [20, 35].

Vaccination

The Hepatitis B vaccine is the foundation of Hepatitis B prevention. The vaccine, available since 1982, has an excellent safety record and is 95% effective in preventing infection. It confers protection for at least 20 years, and in some cases may even be lifelong [20].

The HBV vaccine was included in the South African EPI programme in 1995 and is given at 6, 10 and 14 weeks of age [39]. The coverage of the third dose of the Hepatitis B vaccine in South

Africa was less than 75%, according to the 2012 WHO estimates [40]. However, this may be an overestimate of coverage, and it has been recommended that high quality coverage surveys be conducted, to obtain an accurate assessment [22].

HBV vaccination is recommended in the following individuals [39]: all infants, through the EPI; infants and adolescents not previously vaccinated; and individuals at increased risk of HBV infection as a result of percutaneous or mucosal exposure to blood or blood products, as well as those at risk of more severe infection. These include: healthcare workers (including student healthcare workers and domestic workers in healthcare facilities), injection drug users, MSM, patients in haemodialysis or oncology units, transplant candidates, household contacts and sexual partners of HBsAg-positive individuals, those receiving frequent blood or blood product transfusions, post exposure prophylaxis following occupational or sexual exposure and those with HIV or chronic Hepatitis C [20, 35].

1.2.3 HCV

Epidemiology

Globally, 150 million people are chronically infected with HCV and are at risk of developing cirrhosis and/or hepatocellular carcinoma. About 3–4 million people are infected with HCV annually, of which more than 350 000 people die due to liver related disease [1, 41].

The estimated worldwide prevalence of HCV infection is 2.2%. The geographic differences in the prevalence of HCV infection (similar to HBV), are described: low prevalence (1.0-1.9%), moderate prevalence (2-2.9%), and high prevalence (>3%), However the regions differ from those for HBV [1, 41].

Regions of low HCV prevalence are North America, northern and Western Europe. Countries such as Canada, Germany, France and Australia report a 1% HCV prevalence [4]. Illicit injection drug use is the predominant mode of transmission in most low prevalence areas [1, 41].

The highest global HCV prevalence is in Asia, followed by Africa with the second highest prevalence [3]. Countries in Asia with a high HCV prevalence include China (3.2%) and Pakistan

(2.4-6.5%) [4]. HCV prevalence in sub-Saharan Africa is an estimated 5.3%; Egypt has the highest reported prevalence (22%) [42].

In South Africa, there is a wide variation in HCV prevalence, depending on age, gender, race, geographic location and risk groups.

HCV prevalence increases with age, with a higher prevalence reported in the older than 40 year age group [42].

HCV sero-prevalence in the blood donor population was found to be 0.16%, 0.34%, 0.75%, and 0.22% for whites, Asians, Blacks, and Coloureds respectively [43].

HCV antibodies were found in 1.8% of healthcare workers in a large urban referral hospital in South Africa [23]. The prevalence of HCV in a KZN study of urban and rural populations was 1.7% (95% CI 0.0- 3.6%) and 0.9% (95% CI 0.1-1.7%) respectively [44].

In high risk cohorts (those with liver disease, receiving multiple blood transfusions or blood products, on dialysis and renal transplant patients), the estimated HCV prevalence was 4.3-65% (mean of 23.5%). In low risk cohorts (such as blood donors) the estimated prevalence was 0.1% [42].

There are few representative HCV prevalence studies in South Africa. No cross sectional population surveys are available and existing studies are limited geographically or to specific groups (e.g. high risk cohorts).

Transmission

HCV is ten times more infectious than HIV and is transmitted through contact with the blood or bodily fluids from an infected individual, though in 30-40% of infections the routes of transmission remain unknown. There are multiple routes of transmission (iatrogenic, injection drug use, mother to child, and sexual) [1, 41].

Iatrogenic transmission occurs via contaminated blood transfusions, blood products and organ transplants, contaminated syringes and needle-stick injuries [1, 41].

In high income countries, iatrogenic and injection drug use comprise the most important mechanisms for transmission. In sub-Saharan Africa, there are relatively few injection drug users. However, in this region, the high prevalence of unsafe iatrogenic injections within healthcare settings may account for significant HCV transmission. In South Africa, due to the screening and testing of blood and blood products, the risk of HCV transmission through blood donation is very rare (0.1%) [42].

HCV may be transmitted through sexual intercourse with an infected person, or from mother to infant which is less common. Transmission is estimated to be less than 5% for each mode [42].

Clinical

Hepatitis C is a hepatotropic virus which causes liver disease. HCV infection can range in severity from a mild illness to severe life threatening disease. Approximately 75-85 % of those newly infected develop chronic infection and 60-70% of chronically infected people develop liver disease; 5-20% develop cirrhosis and 1-5% die from cirrhosis or hepatocellular carcinoma. Studies have shown a link between HCV and 25% of all hepatocellular carcinoma patients [3, 45].

Diagnosis

This is based on either antibody detection (HCV IgG), or testing for HCV RNA. Antibody detection is commonly used however it cannot differentiate between acute and chronic infection. The presence of antibodies against HCV indicates that a person either is or was infected. The presence of antibodies is not protective, unlike for HBV. Confirmatory tests require the use of RNA testing [3].

Surveillance

A diagnosis of Hepatitis C is a notifiable condition in South Africa (as described previously for Hepatitis B).

Treatment

Treatment for HCV infection includes the use of antiviral drugs. However, access to treatment is limited by high costs and the lack of availability of resources, especially in low to middle income countries [3].

Prevention

There is no vaccine for HCV. Infections can be prevented by avoiding unsafe injections, blood products and healthcare waste, illicit drug use, unprotected intercourse, sharing of sharp personal items, tattoos and piercings [3].

WHO recommends HCV screening for the following: people who received blood, blood products or organs before implementation of HCV screening; current or former injection drug users; long-term haemodialysis patients; health-care workers; and people living with HIV [3].

1.2.4 HIV and HBV co-infection

Epidemiology

Globally, 2-4 million people are co-infected with HIV and chronic HBV. These co-infection estimates are influenced by age, geographic differences and the prevalence found in high risk populations [1].

Western Europe has a low prevalence of HIV and HBV infections. The low HBV prevalence is due to most HBV infections being acquired in adulthood when chronicity is less likely [1].

Sexual and injection drug use exposures are responsible for most HIV and HBV infections in high income countries. However, chronic HBV infection may be more than ten times higher than the population prevalence among some HIV positive individuals in selected high risk groups [1].

Heterosexual transmission is the predominant mode of transmission for HIV in sub-Saharan Africa. The high prevalence of chronic HBV infection is due to perinatal and early childhood transmission. HBV infection acquired at an early age is more likely to progress to chronicity. This results in a high prevalence of chronic HBV infection among the adolescents and adults at risk for HIV [1].

The epidemiology of both HIV and HBV has been studied in various countries in sub-Saharan Africa, but relatively few studies have examined the burden of HIV/HBV co-infection, and the effect that HIV/AIDS in the region may have on the epidemiology of HBV [5].

Clinical

The natural history of HBV is modified by HIV. Those with co-infections have higher rates of persistence and relapse (re-emergence of HBsAg) and more severe and rapid disease progression (including the development of hepatocellular carcinoma). Acute HBV infection may progress to chronicity in the presence of HIV [46]. About 25% of HIV/HBV co-infections will become chronic, compared to 5% of chronic infections in those without HIV [47].

HIV/HBV co-infection requires individual management of patients, as some ARV drugs (Tenofovir, Lamivudine and Emtricitabine) display anti-HBV activity [48].

Immune reconstitution, following initiation of ARVs, can lead to potentially life threatening flares of Hepatitis B in HIV/HBV co-infected individuals [39].

Mother to child transmission in co-infected pregnant women is important. The high HBV viral loads in the mother can lead to transmission to the infants, irrespective of infant immunisation status. Furthermore, in HIV/HBV co-infected women, there may be a decrease in the transfer of protective Hepatitis B antibodies from mother to child. These women could also have actively replicating HBV, which they are likely to transmit to their new-borns [20].

HIV/HBV co-infected patients lose protective antibodies (HBsAb) faster than HBV infected patients without HIV (40% loss in 1 year vs 5% loss in 1 year, respectively) [49, 50]. The loss of protective immunity may lead to HBV reactivation, or exposure to new HBV infections [48].

1.2.5 HIV and HCV co-infection

Epidemiology

The prevalence of HIV/HCV co-infections varies in high income settings (North America and Europe), depending on the nature of the cohorts [4]. In cohorts with a single predominant risk factor for HIV acquisition, the proportion co-infected with HCV depends on that risk factor, e.g. HIV/HCV co-infection among urban injection drug users ranged from 84% to 88% [4]. In contrast, HIV-positive men, whose primary HIV risk factor was sex with other men, had a lower prevalence of HCV infection (3.7%-6.6%) [4].

There is less published data on the prevalence of HIV/HCV co-infection in low to middle income settings. Injection drug use is less common behaviour and heterosexual transmission accounts for most new HIV cases. There are few HCV sero-prevalence studies among those who acquire HIV through heterosexual transmission, or through exposure to unsafe medical injections [4]. A review of studies conducted in high risk groups found virtually no association between the prevalence of HIV and HCV [42]. There is a paucity of population-based data on the prevalence of HIV/HCV co-infection [4].

Clinical

HIV co-infection was associated with an accelerated progression of liver disease, increased risk of cirrhosis and hepatocellular carcinoma and decreased survival among HCV infected individuals, prior to the introduction of ART [4]. HCV is associated with a delayed recovery of CD4 counts, and may act as a potential risk factor for drug related hepatotoxicity, following commencement of ART [4, 51].

1.2.6 HBV and HCV co-infection

Epidemiology

Population-based sero-prevalence data on HBV/HCV co-infection is unavailable. Existing studies focus on high-risk groups e.g. chronic liver disease patients and injection drug users. Studies in high income settings (such as New Zealand and Italy) describe HBV/HIV co-infection prevalence ranging from 7% to 10% [4, 52, 53].

In low to middle income settings where HBV is highly endemic (such as in The Gambia) 3.8% of hepatocellular carcinoma patients were found to be co-infected [4, 54]. A population-based survey in an urban area in Pakistan reported a low prevalence (0.6%) of HBV and HCV co-infection [4, 55].

Clinical

The proportion of HBV/HCV co-infected individuals influences the chronic liver disease burden. HBV/HCV co-infection in chronic hepatitis patients is associated with more severe liver disease than in chronic hepatitis patients with HCV infection alone [4, 56]. A meta-analysis found an association between HBV/HCV co-infection and hepatocellular carcinoma, suggesting a synergistic effect between the two viruses in causing hepatocellular carcinoma [4, 57]. Liver related mortality was increased in HIV positive patients dually infected with HBV and HCV [4].

1.3 STATEMENT OF THE PROBLEM

The prevalence of HBV and HCV is higher in HIV positive individuals due to shared transmission routes. HIV positive individuals have longer life expectancies as a result of the availability of ART. Therefore, morbidity and mortality due to HBV and HCV related conditions are becoming increasingly prominent among HIV positive individuals. Co-infected patients have more severe liver disease and increased side effects from ARVs [58-60].

It is therefore important to have epidemiological data on co-infection in HIV and HBV/HCV infected individuals. The data may be used to estimate the impact of hepatitis co-infections in HIV positive individuals, which will guide policy makers in terms of screening and prevention programs. There is a need for accurate and reliable epidemiological data, especially in a South African setting in order to prevent and control infection, transmission and spread [5].

There is limited data on HIV and HBV/HCV co-infections in KZN, despite the high HIV prevalence in this population. Existing studies in this region were performed early in the HIV epidemic, prior to the introduction of ART, often in specific high risk groups with small sample numbers, and before the availability of validated laboratory tests [5].

With a view to adding to the epidemiological data on HIV and HBV/HCV co-infections, this retrospective laboratory database study was conducted in the Department of Virology Laboratory (National Health Laboratory Service) at Inkosi Albert Luthuli Central Hospital in Durban to determine the prevalence of HIV and HBV/HCV co-infections in KZN from 2002 to 2010.

1.3.1 Research Questions

1.3.1.1 What is the sero-prevalence of HIV, and HBV/HCV co-infections in KZN from 2002 to 2010?

1.3.1.2 How does the sero-prevalence of HIV, HBV and HCV vary in terms of age, gender and between KZN health districts from 2002 to 2010?

1.3.1.3 What is the sero-prevalence of HBV and HCV co-infections in KZN from 2002 to 2010?

1.4 PURPOSE OF THE RESEARCH

The purpose of the study was to describe HIV and HBV/HCV co-infections in KZN from 2002 to 2010 using a laboratory database, to provide public health recommendations.

1.5 SPECIFIC OBJECTIVES OF THE RESEARCH

1. To describe the socio-demographic profile (age, gender, district of residence) of the study population;
2. To describe the sero-prevalence of HIV, HBV and HCV among the study population;
3. To describe the sero-prevalence of HIV, HBV and HCV in terms of age, gender and KZN health district, from 2002 to 2010;
4. To describe co-infection between (a) HIV and HBV, (b) HIV and HCV and (c) HBV and HCV.

1.6 ASSUMPTIONS UNDERLYING THE STUDY

- The study population is representative of individuals attending public health facilities in KZN.
- The data entered into the laboratory database was done accurately, and with minimal error.
- The results of tests were valid.

1.7 OPERATIONAL DEFINITIONS USED IN THE STUDY

- Sero-prevalence – number of persons in this study population who have a positive serological test for a specific disease [61].
    - HIV sero-prevalence is defined as the percentage of individuals testing positive for either HIV antibodies or HIV antigen.
    - HBV sero-prevalence is defined as the percentage of individuals testing positive for HBsAg.
    - HCV sero-prevalence is defined as the percentage of individuals testing positive for HCV IgG.

- Age – defined as the age at which the individual had the first test for HIV, HBV or HCV, recorded in the database.

- Health district – determined by the health facility location from which the specimen was sent.

1.8 ORGANISATION OF THE REPORT

This dissertation is divided into six chapters.

Chapter one provides an overview of HIV, HBV and HCV globally and locally. This chapter also outlines the research questions, main objectives and purpose of this study.

Chapter two outlines the body of knowledge related to HIV/HBV, HIV/HCV, and HBV/HCV co-infection. Literature pertaining to each of these topics is critically analysed.

Chapter three describes the methods undertaken in this study. This includes study design, study population, data sources, variables, statistical analysis, internal validity and external validity (generalisability), bias and limitations associated with the study.

Chapter four presents the results of the study. The study population is described which is followed by the overall sero-prevalence of HIV, HBV and HCV. Sero-prevalence for each of the viruses is further described in terms of age, gender and KZN health district from 2002 to 2010. The associations between HIV and HBV, HIV and HCV, and HBV and HCV are determined.

Chapter five outlines the findings of the study and discusses these results in relation to previous studies.

Chapter six provides recommendations and conclusions based on the results of the study.

1.9 SUMMARY

HIV, HBV and HCV are important global public health problems. This chapter has provided a background for each of these viruses, with a focus on global and local epidemiology and disease burden.

2 CHAPTER II: LITERATURE REVIEW

2.1 INTRODUCTION

Several studies have documented the prevalence of HIV and HBV/HCV co-infections in sub-Saharan Africa. However, these studies are limited by small numbers and specific high risk cohorts. Furthermore, a number of these studies were conducted early in the HIV epidemic and prior to the introduction to ART.

This study contributes to the epidemiological data on HIV and HBV/HCV co-infections in KZN.

2.2 PURPOSE OF THE LITERATURE REVIEW

The purpose of the literature review was to examine the published literature on the prevalence of HIV/HBV, HIV/HCV and HBV/HCV co-infections in South Africa.

2.3 SCOPE OF THE LITERATURE REVIEW

The scope of the literature review focused on studies that dealt with the prevalence of HIV/HBV, HIV/HCV and HBV/HCV co-infections in South Africa. Selected prevalence studies from sub-Saharan Africa were also reviewed, for the purposes of providing an appropriate context,.

2.4 SOURCES OF LITERATURE REVIEWED

The *PubMed* database was searched for studies between 1980 and 2013 pertaining to the prevalence of HIV/HBV, HIV/HCV and HBV/HCV co-infections.

The following search terms were used to find citations relating to the prevalence of HIV/HBV, HIV/HCV and HBV/HCV co-infections: “Hepatitis”, “HIV”, “Hepatitis B”, “Hepatitis C”, “co-infections”, “epidemiology” and “prevalence”.

2.5 LITERATURE REVIEWED

2.5.1 Prevalence of HIV/HBV co-infection

Sub-Saharan Africa

A summary of the studies described in the literature review, is provided in Table 1.

A systematic review and meta-analysis of 60 studies (12 639 individuals) conducted in 18 sub-Saharan African countries reported a median HBsAg prevalence of 12.10% (range 3.9%-70.0%) in HIV positive individuals [5]. The weighted mean HBsAg prevalence (based on study size) was higher at 14.90% [5].

The Risk Ratio (RR) for having a positive HBsAg in people with HIV, compared to those without HIV, was 1.40 (95% CI 1.16-1.69%), which indicates a 40% increased risk for a positive HBsAg in those with HIV, compared to those without HIV [5]. The tau squared statistic (where τ^2 >0.1 indicates substantial heterogeneity) was 0.2 [5].

There was no significant difference in HBeAg positivity between those with HIV and those without (17.10% vs 15.40%, p = 0.5), based on the findings of thirteen studies [5].

There are a number of limitations that weaken the internal validity of the study [5]. These include the observational nature of the reviewed studies (retrospective and cross sectional only) and the demonstrated heterogeneity between studies. Furthermore, the pooled prevalence over a large and diverse geographical area may not be a true estimate of the HBV prevalence in those with HIV [5].

The use of HBsAg as a surrogate marker for HBV infection may also underestimate the true prevalence of HBV infection, by overlooking the possibility of 'occult HBV infections' (positive HBV DNA, in the absence of a positive HBsAg), especially in those with HIV [5]. However, 'occult HBV' is a rare finding and may have a negligible effect on prevalence [20].

The lack of an observed association between the prevalence of HBsAg and HIV may be due to the small number tested (n = 495) [5].

There may be an inherent selection bias present, as only published studies were included for review; the authors did not include data presented solely at conferences or publications in regional journals [5].

The generalisability of the systematic review by Barth is limited by most of the studies being set in urban areas, the majority of participants being female and selected study populations (blood donors, pregnant women or sex workers) [5].

The strengths of the study are based on it being the largest systematic review and meta-analysis of Hepatitis B/C and HIV co-infection in sub-Saharan Africa, a region which lacks reliable epidemiological data. The findings suggest a considerable difference in the prevalence of HBV in HIV positive individuals across the region. This has implications for public health prevention and treatment strategies [5].

South Africa

Lodenyo described a HIV/HBV co-infection prevalence of 6.0% in a prospective cohort of 100 patients with AIDS who were admitted to a tertiary public sector hospital in urban Johannesburg, prior to the national rollout of ART [62]. More than a third (35%) of patients had evidence of past HBV infection; and half of those with HBsAg positivity were also positive for HBeAg [62]. The age range of the patients was 16 to 54 years (mean age = 34.6 years; Standard Deviation (SD) = 7.5 years) [62]. The gender distribution was 52% males, and 48% females [62]. The mean CD4 count was 141.5 cells/µl (SD = 168.6 cells/µl) [62].

The findings of the study were comparable to those from higher income countries, and the relatively low HBsAg prevalence indicated that the patients were infected when still immunocompetent [62]. The generalisability of this study was limited by the small number of enrolled patients, and that the patients themselves represented a select group (those who were admitted to hospital with a diagnosis of AIDS) [62].

In 2009, Firnhaber reported a HBsAg prevalence of 4.78% in a prospective cohort study of 502 HIV positive outpatients attending an urban HIV clinic in Johannesburg [63]. Nearly half (47%) of the patients in this study showed some evidence of HBV exposure, which was similar to the findings of Lodenyo [62]. However, in contrast to the latter study, there was no demonstrated

association between HBsAg and HBeAg [63]. The female to male ratio was 2.5:1, with a mean age of 37 years (SD 9.1 years) and a CD4 count of 128.6 cells/µl (SD 84.4 µl) [63]. The risk of HIV/HBV co-infection was not significantly different in terms of age, gender, race or CD4 count [63].

A limitation in both the Lodenyo and the Firnhaber studies was the low CD4 count [62, 63]. It is possible that the presence of a severely immunocompromised state (characterised by a low CD4 count) could have potentially decreased the production of antibodies to HBV, leading to a misclassification bias in the diagnosis of HBV [63].

Previous studies have suggested a higher prevalence of HIV/HBV co-infection in rural compared to urban areas [64]. HBsAg prevalence among HIV positive adults was found to be 20% in a cohort of gold miners from a rural area [58], compared to the 5-6% HBsAg prevalence in HIV infected urban cohorts [62, 63].

Hoffman, in a retrospective cohort study, described a 20% HBsAg prevalence in 537 patients enrolled in a workplace ART program in a rural mining community [58]. The majority of the patients (94%) were male, with a median age of 41 years, interquartile range (IQR) 36-46 years, and a median CD4 count of 146 cells/µl (IQR 79-224 cells/µl) [58].

The first limitation of the study was that general illness and malnutrition levels of mine workers would not be comparable to that found in other low income settings. Secondly the predominantly male cohort was from a number of African countries, therefore the observed HIV/HBV co-infection prevalence may not be generalisable to the rural South African population [58].

In contrast to the Hoffman study [58], Barth described a very low HBsAg (0.41%) prevalence in 248 ARV naïve patients attending a rural clinic in Limpopo [65]. The majority of the patients were female (63.71%) with a median CD4 count of 273 cells/mm^3 (IQR 91-393 cells/mm^3) [65]. A possible reason for the low HBsAg prevalence was that the community may have had limited contact with high endemic areas due to geographic, ethnic or cultural factors [65]. This is in addition to the limitations associated with a predominantly female cohort and a small number of patients [65].

Boyles described a HBsAg prevalence of 7.14% in 1765 HIV positive patients, enrolled on ART at a rural clinic in Eastern Cape. One quarter of the patients were males with a median age of 31.8 years (IQR 26.3-39.2 years) and a median CD4 count of 207 cells/µl (99-69 cells/µl). Age was not found to be associated with HBsAg [64].

This study was the first to suggest that being male is a risk factor for HIV/HBV co-infection, with a crude Odds Ratio (OR) of 2.64 (95% CI 1.76-3.95%) and an adjusted OR of 2.59 (95% CI 1.68-4.00%), $p<0.001$ in male patients with HIV/HBV co-infection [64].

There are a few laboratory based HIV/HBV prevalence studies in South Africa [66-68]. These studies are generally retrospective in nature, have small study numbers and involve the analysis of stored sera.

Mphahlele reported a HBsAg prevalence of 16.2% in 295 stored sera samples from 167 HIV positive and 128 HIV negative patients from a tertiary hospital in Limpopo province [68]. This was a retrospective, unmatched case control laboratory based study of stored sera conducted at a tertiary hospital in Limpopo. None of the specimens were from patients vaccinated with the HBV vaccine, or on ARVs. The mean age was 34.4 years; range was 15-78 years, and the distribution of males to females was almost 50% [68].

There was a higher prevalence of HBsAg in the HIV negative compared to the HIV positive specimens (35.2% vs 16.2%), even though the HIV positive and HIV negative groups were exposed equally to HBV [68].

These paradoxical findings could be attributed to the presence of a selection bias, as HIV negative specimens from the same tertiary hospital setting were used as controls. The bias could be attributed to the HIV negative specimens being from patients with chronic liver disease who were attending the gastroenterology unit at the tertiary hospital. Thus a greater number of HIV negative patients would have been HBsAg positive due to the nature of their pre-existing disease. The study does not comment on any matching of cases and controls having occurred, which could have further contributed to the presence of bias in the findings.

Lukwhareni documented the findings from a retrospective laboratory based study of stored sera from 192 HIV positive patients in the same tertiary hospital setting [67], as in the study by

Mphahlele [68]. The mean age was 37.1 years (range of 14-68 years), and 68% were males [67]. The CD4 cell counts ranged from 2-1069 cells/µl, with a mean count of 116 cells/µl [67]. The sera was from patients who were not yet started on ART [67].

The study found a 22.9% HBsAg sero-prevalence, with an overall 63% having been exposed to HBV. This was higher than the prevalence reported by Mphahlele [68].

Burnett described a statistically significant difference in the prevalence of HBsAg (39.2% vs 30.1%; OR = 1.49, 95% CI 1.19 – 1.87, p<0.0004) between HIV positive (n = 710) and HIV negative (n = 710) pregnant South African women [66]. The study design was a retrospective, anonymous, matched case–control which was conducted on the stored sera of pregnant women that attended public antenatal clinics in Limpopo and the North West Province from 1999 to 2001 [66].

A major bias in the study is that the study population included only pregnant women that attended antenatal clinics. This excluded all non-pregnant women and women who did not attend antenatal clinics. A further possible source of bias is the over representation of healthy HIV positive pregnant women who regularly use the antenatal facilities [66]. Thus, the study findings are not generalisable to the general population.

The literature review of studies on HIV/HBV co-infection highlighted the following: the prevalence of HBsAg varies depending on geographic location, sex, HIV status, age; the type of study design, the timing of the study and the location of the study. This emphasizes the need for population level HIV/HBV co-infection prevalence data in South Africa.

2.5.2 Prevalence of HIV/HCV co-infection

Sub-Saharan Africa

A systematic review and meta-analysis conducted by Barth reported 6.90% (9029 participants) were co-infected with HIV and HCV [5]. The median prevalence across studies was 4.80% (range 0.0-22.2%) [5].

The RR for having HCV in those with HIV, compared to those without HIV was 1.60 (95% CI 1.05-2.45); HIV positive individuals had a 60% increased risk of having HCV, compared to those without HIV. The included studies were highly heterogeneous ($\tau^2 = 0.6$).

The limitations which weaken the internal validity of the study have been described previously for HBV and are also applicable here [5]. These include the observational nature of the reviewed studies (retrospective and cross sectional only) and the demonstrated heterogeneity between studies. The pooled prevalence over a large and diverse geographical area may not be a true estimate of the HBV prevalence in those with HIV [5].

Furthermore, a non-differential misclassification bias (towards the null) may be present in the study, as it is not possible to make a distinction between active and spontaneously resolved HCV infection solely using HCV serology [5]. Thus the prevalence of HCV may be lower than the reported prevalence [5].

A contrasting view from Madhava, in a review of the HCV prevalence in sub-Saharan African countries is relevant here [42]. In this review, there was almost no association found between HCV and HIV in 20 studies that examined HIV/HCV co-infection [42, 69-71]. It was also noted that the countries with the highest HIV infection prevalence had the lowest estimated HCV prevalence [42].

A limitation of the Madhava study is that some of the reviewed studies were conducted on archived blood. Also, some studies did not indicate when the blood samples were collected. This is important due to the changes that have occurred in HCV epidemiology, and the recent improvements in HCV diagnostic specificity and sensitivity [42]. Another reason for the differences in findings between the Madhava [42] and the Barth [5] studies, is that the former was not a systematic review and meta-analysis and was conducted almost a decade prior to the latter study.

South Africa

Several studies have demonstrated a low HCV prevalence (approximately 1%-2%), in HIV-HCV co-infected patients in South Africa [51, 72]. This is in contrast to the finding of a HCV prevalence of 13.4% in patients with HIV, as described by Parboosing [73].

The prevalence of HIV/HCV co-infection was 1.9% in South Africa during a multinational, randomized placebo controlled study assessing the safety and efficacy of the addition of lamivudine to antiretroviral therapy in 1649 participants [51].

The study limitations were as follows: the study was conducted in the 1995, prior to the rollout of ART, and was not specifically designed to examine HIV/HCV co-infection. The majority of the South African participants were Caucasian, which did not reflect the epidemiology of HIV. The study only included those patients with a CD4 count of 25-250 cells/µl, so the findings may not be representative of all levels of immune deficiency; an Alanine Transaminase (ALT) level 5 times greater than upper limit of normal was an exclusion criterion, which possibly underestimated the sero-prevalence of HIV/HCV co-infection [51].

Gededzha documented a HCV sero-prevalence of 1.2% in 653 HIV patients enrolled for ART at a tertiary hospital in Pretoria, from 2004 to 2008 [72]. This study used a retrospective, laboratory based design [72].

Limitations regarding the laboratory diagnosis of HCV were as follows: serological assays did not distinguish between acute, chronic and past infection and the low prevalence of HCV antibodies could be due to immunosuppression of the patients [72] . Other limitations included the use of stored sera, the insufficient sample volumes and that the study was conducted on patients attending a tertiary HIV referral clinic in a hospital setting, which limits its generalisability [72].

Co-infection with HIV and HCV was found to be rare (1%) in a prospective cohort study conducted by Lodenyo on 100 patients (52 males and 48 females, ages 16 to 54 years) with AIDS, admitted to a tertiary hospital in Johannesburg [62]. Limitations of this study were described earlier. These included the small number of enrolled patients and that the patients themselves represented a select group (those who were admitted to hospital with a diagnosis of AIDS) [62].

HIV/HCV co-infection was found to be even lower (0.8%) in a rural cohort of 252 patients in Limpopo [65]. Limitations of the study were described earlier and include the predominantly female sample and the small numbers of patients [65].

In contrast to previous HCV prevalence studies in HIV positive patients, Parboosing reported a significantly higher prevalence of HCV among HIV positive patients as compared to those without HIV (13.4% vs. 1.73% respectively) OR = 8.8 (95% CI 5.4-14.3) ($n = 1937$, $p < 0.001$) [73]. This study was a sero-prevalence survey of all samples submitted for routine HIV testing from selected sentinel sites to a central laboratory which were screened for HCV. The prevalence of HCV was 6.4% and that of HIV, 40.2% ($n = 1937$). Study limitations included a sample bias, as specimens were selected from patients in whom an indication existed for an HIV test, but these patients may also have risk factors for HCV [73].

2.5.3 Prevalence of HBV/HCV co-infection

There are few South African studies that have documented HBV/HCV co-infections.

A case control study of 231 patients being treated for hepatocellular carcinoma at four hospitals in Johannesburg, described a HBV/HCV co-infection prevalence of 8.66% in HBV/HCV co-infected patients [74]. None of the patients with hepatocellular carcinoma were HIV positive [74].

A study of 110 patients with chronic liver disease, that were treated in a tertiary hospital setting in Durban found 1 patient (0.9%) testing positive for both HBV and HCV [43]. None of the patients in the study were HIV positive [43].

Limitations to the generalisability of the findings from the two studies include the lack of HIV positive patients, the period in which they were conducted (early in the HIV epidemic, and prior to the availability of ART); and the lower sensitivity and specificity of the previous assays for the testing of HBV and HCV.

Table 1: Comparison of studies discussed in the literature review

Author	Study setting and study design	Number of participants	Age (years) and Gender of participants	Study population	Test	Sero-prevalence
Barth [5]	sub-Saharan Africa Systematic review and meta-analysis	12639 with HIV/HBV 9029 with HIV/HCV	Age not stated	General and high risk populations	HBsAg HCV IgG	HIV/HBV sero-prevalence 12.1%, RR = 1.40 95% CI (1.16 – 1.69) HIV/HCV sero-prevalence 6.9%, RR = 1.60 95% CI (1.05 - 2.45)
Lodenyo [62]	Tertiary hospital, Gauteng Prospective cohort	100	16-54 years (Range) 52% Male/ 48% Female	Urban, in-hospital patients	HBsAg	6.0% HBV sero-prevalence 1% HCV sero-prevalence
Firnhaber [63]	ARV clinic, Gauteng Cross sectional	537	37 years (Mean) 44% Male/ 56% Female	Urban, outpatients	HBsAg	4.8% HBV sero-prevalence
Boyles [64]	ARV clinic, Eastern Cape Cohort	1765	31.8 years (Median) 25% Male/ 75% Female	Rural, outpatients	HBsAg	7.1 % HBV sero-prevalence
Hoffmann [58]	Workplace ARV clinics, South Africa Prospective cohort	537	44 years (Median) 94% Male/ 6% Female	Mineworkers	HBsAg	19.7% HBV sero-prevalence
Barth [65]	ARV clinic, Limpopo Cohort	248	40.5 years (Mean) 36% Male/ 64% Female	Rural, outpatients	HBsAg HCV IgG	0.4% HBV sero-prevalence 0.8% HCV sero-prevalence
Mphahlele [68]	Tertiary hospital, Limpopo Retrospective, case control, laboratory	295	34.4 years (Mean) 15-78 years (Range 50% Male/ 50% Female	In-hospital patients	HBsAg	16.2% HBV sero-prevalence

	based					
Lukhwareni [67]	ARV clinic, Limpopo Retrospective, laboratory based	192	37 years (Mean) 14-68 years (Range) 32% Male / 68% Female	Outpatients	HBsAg	22.9% HBV sero-prevalence
Burnett [66]	Antenatal clinics, Limpopo and North-West Retrospective, case control, laboratory based	1420	Age not stated 100% Female	Outpatients	HBsAg	6.2% HBV sero-prevalence
Madhava [42]	sub-Saharan Africa Review	605225	Age not stated <20, 20-40, >40 (Age groups)	General and high risk populations	HCV IgG/ HCV PCR	South and East Africa – mean HCV prevalence 3.0% (range 0.9 – 40.0%) HBV/HCV - no association in 20 studies
Amin [51]	South Africa Multinational randomised placebo controlled	1604	18-29, 30-39, 40-49, ≥50 (Age groups) 86% Males/ 14% Females	Outpatients	HCV IgG / HCV PCR	1.9% HIV/HCV sero-prevalence
Gededzha [72]	Tertiary hospital, Pretoria Retrospective, laboratory based	653	Not stated	Outpatients	HCV IgG / HCV PCR	1.2% HIV/HCV sero-prevalence
Parboosing [73]	Regional hospital, Durban Retrospective, laboratory based	1937	36.3 years (Mean) 40% Males/ 59% Females	In-hospital patients	HCV IgG	HIV/HCV sero-prevalence 13.4%, OR=8.8 (95% 5.4-14.3%)
Kew [74]	Hospitals, Gauteng Retrospective case control	231	44.8 years (Mean) 18-82 years (Range) 87% Males/ 13%	In-hospital patients	HBsAg HCV IgG	8.66% HBV/HCV sero-prevalence

			Females				
Soni [43]	Regional hospital, Durban Prospective cohort	110	Higher male to female ratio	48 (Mean) 12-85 (Range)	In-hospital patients	HBsAg HCV IgG	0.91% HBV/HCV sero-prevalence

2.6 SUMMARY

The literature reviewed in this chapter revealed that there is a paucity of studies relating to HIV/HBV, HIV/HCV and HBV/HCV co-infections in South Africa.

3 CHAPTER III: METHODS

3.1 INTRODUCTION

While there is available evidence on HIV and HBV/HCV co-infections in higher income countries, these findings are rarely generalisable to a South African setting, due to the specific high risk cohorts, and the small study numbers.

There is a paucity of data regarding HIV and HBV/HCV co-infection in South Africa. This research described the overall sero-prevalence of HIV, HBV and HCV, in relation to age, gender and KZN health district from 2002 to 2010; and measured the associations between HIV and HBV/HCV and between HBV/HCV.

This chapter describes the type of research carried out. The study design applied is outlined. The study population, data sources, statistical analysis, bias and limitations of the research are described.

3.2 TYPE OF RESEARCH

An epidemiological research study of a laboratory database was conducted.

3.3 STUDY DESIGN

An observational, analytical, retrospective study design was used.

3.4 STUDY SETTING

The study was conducted in the Department of Virology, National Health Laboratory Service (NHLS), at the Inkosi Albert Luthuli Central Hospital, Durban, KZN. The laboratory is accredited by the South African National Accreditation System (SANAS) [75] and is the reference Virology laboratory for the public health sector in KZN. At the time of the study, the laboratory received the majority of specimens for viral tests in KZN (with the exception of 1 hospital that did not send specimens for HIV testing) [76]. There were 72 hospitals, 18 community health

centres and 428 clinics in the KZN public health sector. According to Statistics South Africa (StatsSA), approximately 10% of the KZN population reported having medical aid coverage; the remainder relied primarily on state health-care services [77].

3.5 TARGET POPULATION

The results of this study could be generalized to all individuals attending public health facilities in KZN.

3.6 STUDY POPULATION

Inclusion criteria: All individuals who had a HIV or HBV or HCV serological test result (either a positive, negative or indeterminate result) in the database from January 2002 to December 2010 were included in the study.

Exclusion criteria: All those without a HIV or HBV or HCV serological test result in the database from January 2002 to December 2010.

The study population consisted of 507 834 individuals (i.e. all those with HIV, HBV or HCV test results from 2002 to 2010). All individuals who fulfilled the inclusion criteria were entered into the study, even if one or more data fields were absent.

3.7 SAMPLING

The study did not use a sampling strategy. All the individual test results that fulfilled the inclusion criteria were included in the study.

3.8 DATA SOURCES

3.8.1 Measurement instruments/Data collection techniques

Samples were received in the Department of Virology laboratory accompanied by a request form, containing basic demographic and clinical data. In accordance with standardised procedures, the data was captured onto the Laboratory Information System (LIS) by laboratory data-capturers, using a standard template. The real time data entry was cross checked to identify possible transcription errors, using standard operating procedures in the laboratory

Patients were uniquely identified by hospital number and specimens were uniquely identified by a bar-coded specimen number. The results of laboratory tests for each patient were uploaded electronically into the LIS through an interface between the specimen analyser and the LIS database which is routinely cross checked manually by laboratory staff, as per the standard operating procedures.

The routine diagnostic serological tests which were done included ELISAs for HBsAg, HBsAb, HBeAg, Hepatitis C IgG, and HIV antibody and antigen.

3.8.1.1 Data abstraction

Study data was abstracted from the LIS database, using the following specified criteria:

Laboratory tests for which a result was recorded for HIV, HBV and HCV ELISAs from January 2002 to December 2010.

Demographic information included age, gender and name of health facility from which the blood was sent.

3.8.1.2 Data handling

The data was downloaded from the Inkosi Albert Luthuli Central Hospital information system into Excel® (Microsoft Corporation© Redmond, Washington, USA). A variable for ‘district’

was created by allocating each health facility to the appropriate district, using information from the KZN Department of Health. The following fields were downloaded: hospital number, health facility name, age, gender and laboratory result. A unique record number (distinct from the hospital number) was allocated sequentially to each downloaded record in order to maintain the anonymity of results. The data was imported into the statistical software package (SAS Institute©, Cary, North Carolina, USA).

Duplicate entries, defined as patients (identified by their hospital numbers) who had more than one result for the same test, were removed as follows: when individuals had more than one result for the same test, only one result was analysed: the first positive result when the individual tested positive at least once, and the first negative result, when the individual never tested positive.

3.9 VARIABLES

Demographic variables were allocated as follows:

- Age was a categorical and a continuous variable.

When age was categorized, the categories were labelled 0-1, 2-4, 5-9 etc. The category 0-1 included all individuals from birth to less or equal to 1 year of age. The category 2-4 included all those individuals greater than 1 year, and less than or equal to 4 years of age, and so forth.

- Gender was a categorical variable.

- Health district was a categorical variable.

Serological variables were as follows:

- HIV – HIV antibody or HIV antigen;
- HBV – HBsAg, HBeAg or HBsAb;
- HCV – HCV IgG.

3.9.1 Reliability and validity of the data source

Sample collection, data capture, serological assays and release of results in the Department of Virology were carried out according to accredited procedures. Laboratory methods were validated for diagnostic purposes and appropriate internal and external quality control procedures were in place. Results from automated instruments were interfaced directly with the LIS so to avoid errors due to manual entries of results. A 10% transcription check was performed to minimize errors in situations when manual entry of data is unavoidable [78]. The kits used for the ELISA assays have high sensitivity and specificity. The sensitivities and specificities according to manufacturer's package inserts [79] (ADVIA Centaur®, Siemens Healthcare, Munich, Germany) are shown in Table 2.

Table 2: Sensitivities and specificities of HIV, HBV and HCV assays that were used in this study

Assay	Specificity (%, 95% confidence interval)	Sensitivity (%, 95% confidence interval)
HIV	99.74 (99.60 – 99.84)	100 (99.08 – 100)
HBV	99.90 (99.78 – 99.97)	100 (99.09 – 100)
HCV	99.91 (99.78 – 99.97)	100 (99.18 – 100)

3.10 BIAS AND LIMITATIONS

3.10.1 Selection bias

A pre-existing selection bias is that all the patients in the database represent those visiting public health care facilities in KZN; the database does not include data from private laboratories.

The selection bias present may be due to health seeking behaviour by individuals who visit public facilities and allow or consent for bloods to be taken for testing. These patients may have a different disease profile from those that do not go to health institutions at all, or those that refuse testing, or those that are asymptomatic and do not require testing. Furthermore, there may be variations in the clinical indications for performing the tests on each patient.

This selection bias is unavoidable since this research is a retrospective analysis of pre-existing data in the LIS.

3.10.2 Information Bias

An information bias present in the data is that the physical location does not refer to individual patient's addresses; rather it refers to the health facility at which the bloods was taken. There may also be transcription errors in terms of recording of demographic information such as age or sex.

An information bias relating to the laboratory tests could be due to false positive or false negative results. However, this is unlikely due to the high specificity and sensitivity of the diagnostic assays and the presence of quality controls and algorithms in place for the confirmatory testing of HIV, HBV or HCV.

Any information bias present will most likely be non-differential in nature and will potentially bias results towards the null.

3.10.3 External validity/Generalisability

The findings from this study can be generalized to those who visit public health facilities in KZN.

3.10.4 Confounders

The variables age, gender and health district may be potential confounders in the association between HIV and HBV/HCV sero-prevalence.

3.11 STATISTICAL ANALYSIS

3.11.1 Descriptive methods

Basic procedures in SAS 9.3 (SAS Institute©, Cary, North Carolina, USA) were used to generate descriptive statistics. Graphs were produced in Excel™ 2010 (Microsoft Corporation©, Redmond, Washington, USA).

3.11.2 Analytical methods

Statistical analysis: differences in proportions were determined by the Chi-squared test and OR. For the OR, 95% confidence limits were calculated based on a binomial distribution, using the SAS (SAS Institute©, Cary, North Carolina, USA) PROC FREQ procedure. The significance of changes in sero-prevalence over time was determined by the two-sided Cochrane Armitage Trend test. A p value of < 0.05 was regarded as significant. Statistical advice was sought while planning this study.

3.12 ETHICS

Ethical approval to conduct this study was obtained from the University KwaZulu-Natal Biomedical Research Ethics Committee (BE 038/11) (Appendix A).

Consent from individuals was not sought for this study for the following reasons: informed consent was not required as the data was anonymised, the data was unlinked to patient identifiers, and the retrospective nature of the study.

3.12.1 Permissions

Approval to conduct the study using data stored in the laboratory information system was obtained from the Department of Virology, National Health Laboratory Service (Appendix A).

The study was registered as a research project for the Master of Medicine (Public Health Medicine) with the University of KwaZulu-Natal Postgraduate Education and Research Committee (Appendix A).

3.13 SUMMARY

This epidemiological study was a retrospective analysis of laboratory database. The purpose of the study was to describe HIV and HBV/HCV co-infection in KwaZulu-Natal from 2002 to 2010, using a laboratory database to make public health recommendations. In this chapter, the study population, data sources, statistical analysis, bias and limitations of the study were described.

4 CHAPTER IV: RESULTS

4.1 INTRODUCTION

The purpose of this retrospective study of a laboratory database was to describe HIV and HBV/HCV co-infection in KZN from 2002-2010. This was done by describing the overall sero-prevalence of HIV, HBV and HCV; and in terms of age, gender and KZN health district from 2002 to 2010; followed by measuring the associations in sero-prevalence between HIV and HBV; HIV and HCV; and HBV and HCV.

The study population comprised of all individuals who had a HIV or HBV or HCV serological test result (either a positive, negative or indeterminate result) in the database, from January 2002 to December 2010.

4.2 STUDY SAMPLE

The study did not use a sampling strategy. All the individuals who fulfilled the inclusion criteria were included in the study.

4.3 PRESENTATION OF DATA

4.3.1 The socio-demographic profile (age, gender, district of residence) of the study population

This study analysed the results of 507 834 serological assays (Table 3). The mean age when individuals had their first HIV, HBV or HCV test, was 29.34 years, 95% CI (29.30-29.39 years) (Table 7 in Appendix B). Most of the results were from individuals in the 25-30 and 35-40 year age groups (Table 8 in Appendix B). Further details of the distribution of tests per age category for each of the viruses is shown in Table 8 in Appendix B.

More females than males were tested for each of the viruses (Table 9 in Appendix B) i.e. 58.84% of females had HIV tests compared to 35.62% of males; 55.73% of females had HBV

tests compared to males (33.53%) and 53.86% of females had HCV tests compared to 33.99% of males (Table 9 in Appendix B).

Results were available for all 11 KZN health districts. The majority of HIV tests (67.01%), HBV tests (66.79%) and HCV tests (55.88%) were from eThekwini district (Table 10 in Appendix B).

Table 3: Number and % of individuals with HIV, HBV or HCV serological tests in the study population, from 2002 to 2010

Number of individuals	**Number, % of study population***
N = 507 834 (study population i.e. individuals who had HIV, HBV or HCV serological tests from 2002 to 2010)	
Individuals with a HIV test	266 411 (52.46)
Individuals with a HBV test	266 306 (52.44)
Individuals with a HCV test	79 216 (15.59)

(*> 100%, as some individuals had a serological test for more than one of the above viruses)

4.3.2 HIV, HBV and HCV sero-prevalence for the study population

The overall sero-prevalence for HIV was 47% (95% CI 46.81-47.19%), HBV was 12.05% (95% CI 11.92-12.17%) and HCV was 4.13% (95% CI 3.99-4.27%) (Table 4).

Table 4: HIV, HBV and HCV sero-prevalence for the study population from 2002 to 2010

Test	HIV positive	HBV positive	HCV positive
	N = 266 411* (excluding 4346 or 1.63% indeterminate results)	**N = 266 306* (excluding 4804 or 1.80% indeterminate results**	**N = 79 126* (excluding 2562 or 3.23% indeterminate results)**
Number	125 215	32 078	3270
Sero-prevalence (%, 95% CI)	47.00 (46.81-47.19)	12.05 (11.92-12.17)	4.13 (3.99-4.27)

(*Number of individuals tested for the respective virus)

4.3.3 Sero-prevalence of HIV, HBV and HCV in terms of age, gender, health districts and time period

Age and Gender

The highest sero-prevalence for HIV and HCV was in the 30-35 year age group, 66.44% and 5.03% respectively. The highest sero-prevalence for HBV was in the 20-25 year age group (15.74%) (Tables 11, 12, 13 in Appendix B).

The sero-prevalence for HIV was higher in females when compared to males (47.81% vs 45.98%, $p < 0.0001$) (Table 14, in Appendix B). For both the hepatitis markers, sero-prevalence was higher in males than in females (HBV: 15.54% vs. 9.91%, $p<0.0001$ and HCV: 4.38% vs. 3.8%, $p<0.0001$) (Table 14 in Appendix B).

Figures 1-3 and Tables 15-20 (Appendix B) show the sero-prevalence per age category for each gender. The Figures and Tables illustrate that the peak prevalence of HIV and HCV in females occurs at an earlier age than males, while the opposite is true for HBV, when the age categories > 70 years of age are excluded (few or no patients and wide confidence intervals) .

The 0-1 year age group shows a HBV sero-prevalence of 9.45% (Figure 2, and Table 12 in Appendix B).

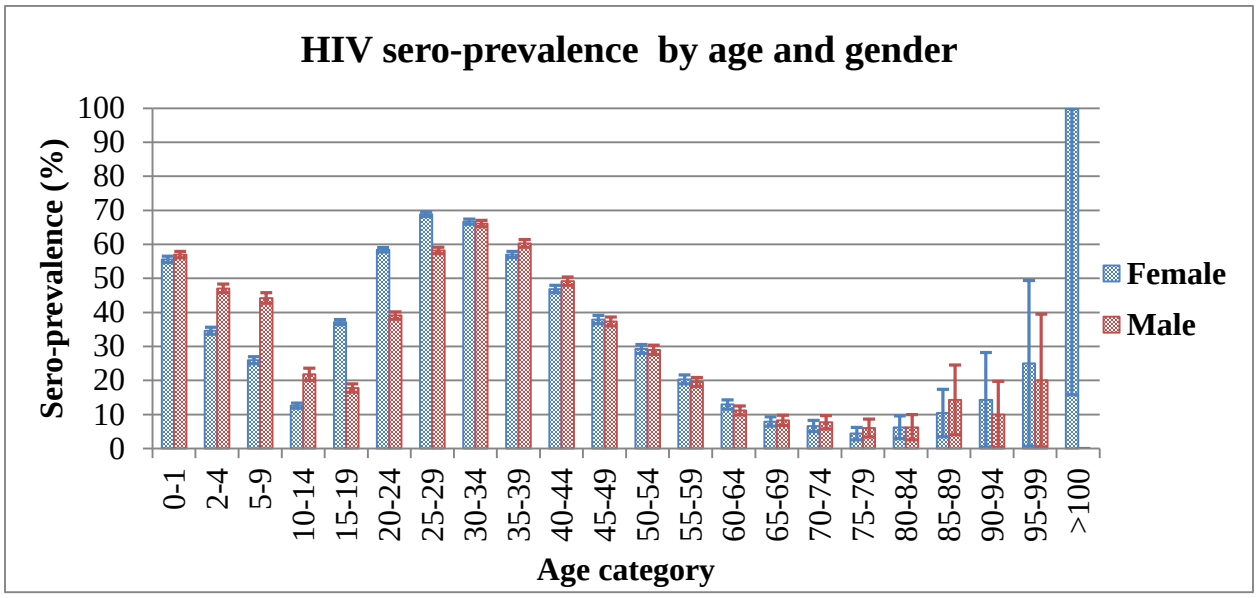

Figure 1: HIV sero-prevalence (with 95% CI) by age and gender for the study population from 2002 to 2010

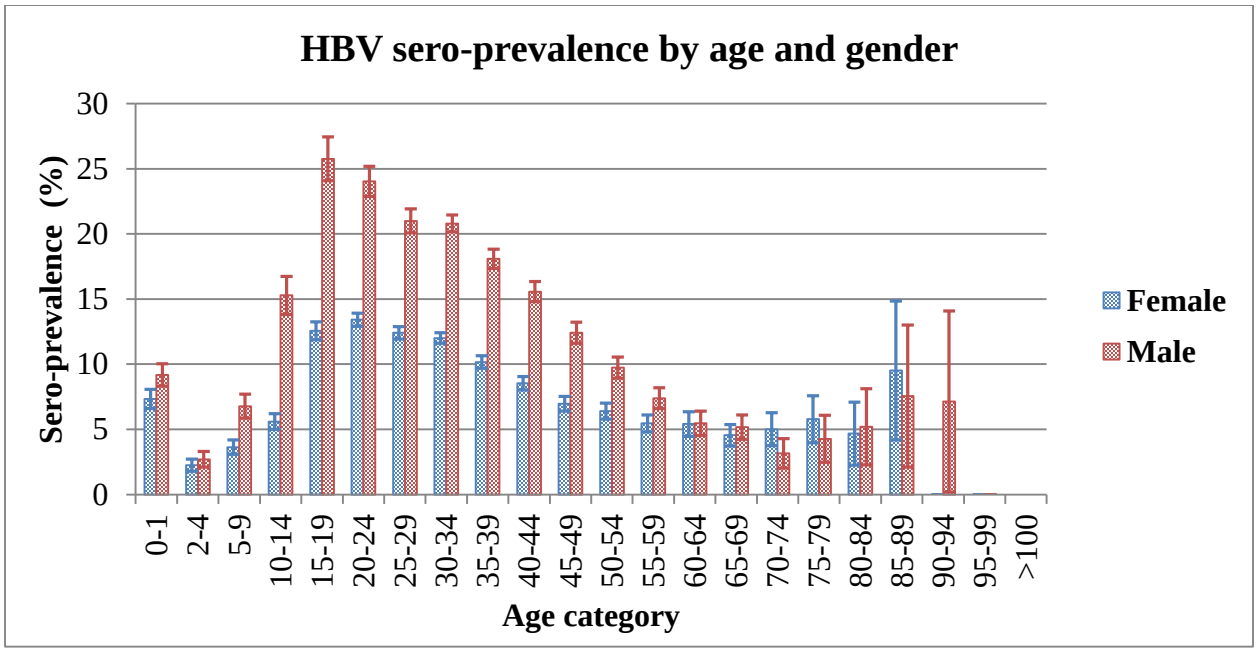

Figure 2: HBV sero-prevalence (with 95% CI) by age and gender for the study population from 2002 to 2010

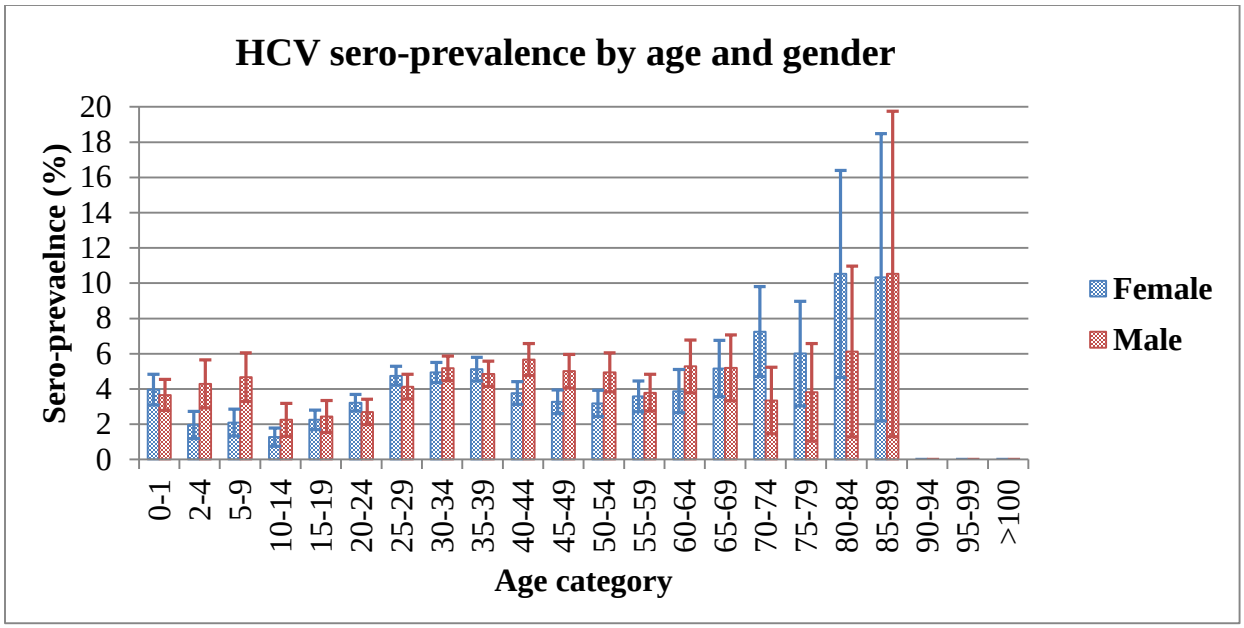

Figure 3: HCV sero–prevalence (with 95% CI) by age and gender for the study population from 2002 to 2010

Health District

The variations in sero-prevalence for HIV, HBV and HCV per health district are shown in Figure 4 and Tables 21-23 (Appendix B). The highest HIV sero-prevalence was in uThukela (87.27%), the highest HBV sero-prevalence was in Amajuba (38.94%), and Zululand recorded the highest HCV sero-prevalence (6.30%).

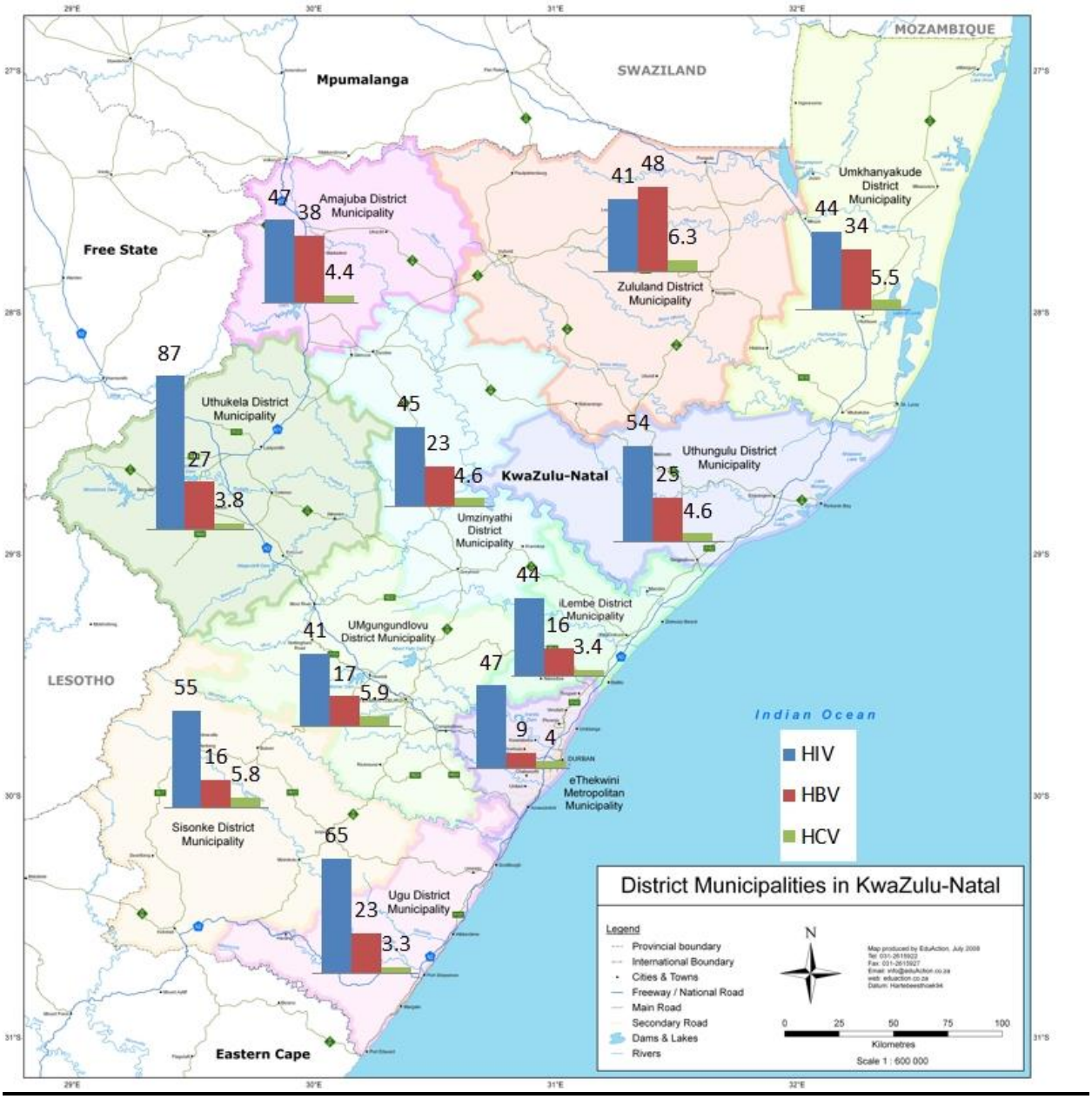

Figure 4: HIV, HBV and HCV sero-prevalence in 11 KZN health districts from 2002 to 2010 (Source of map [80])

Time period 2002 to 2010

Fig 5-8 and Tables 24-26 (Appendix B) show that the sero-prevalence of HIV and HBV has decreased significantly over time ($p<0.0001$). The decrease in HIV sero-prevalence commenced from 2004.

In contrast, the sero-prevalence of HCV did not change significantly over time (p>0.5).

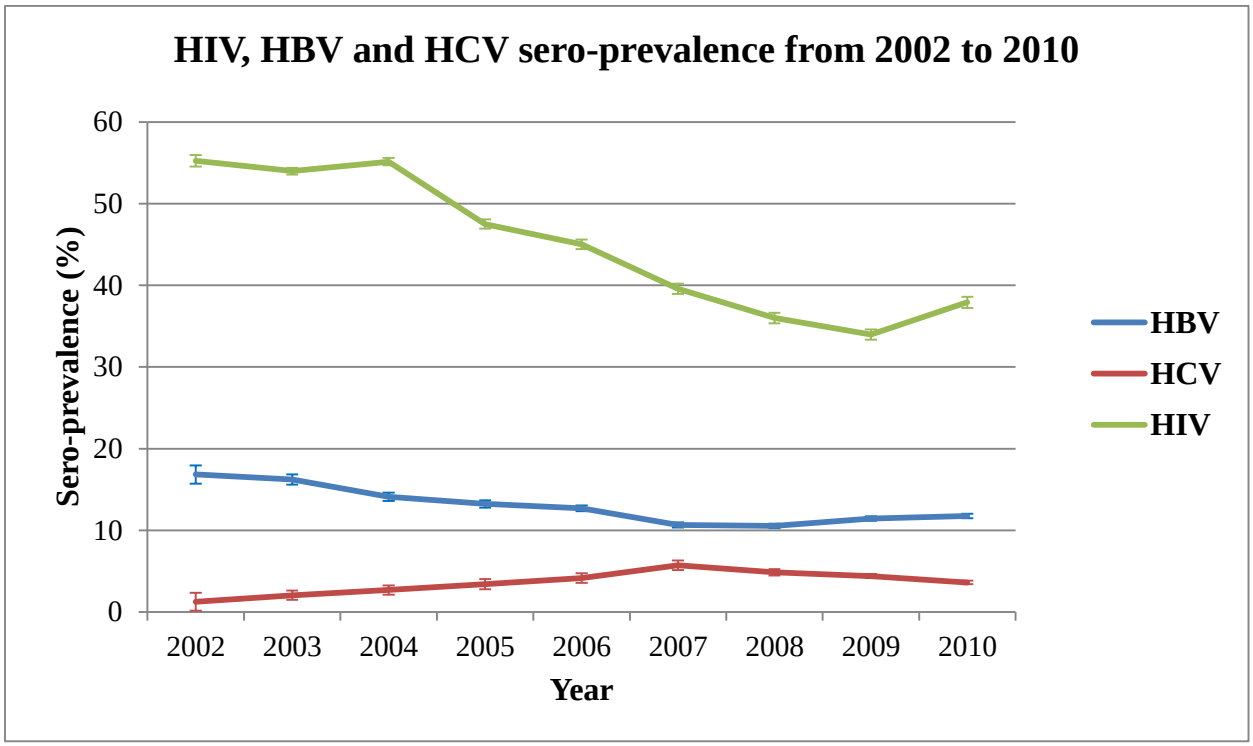

Figure 5: HIV, HBV and HCV sero-prevalence for the study population from 2002 to 2010

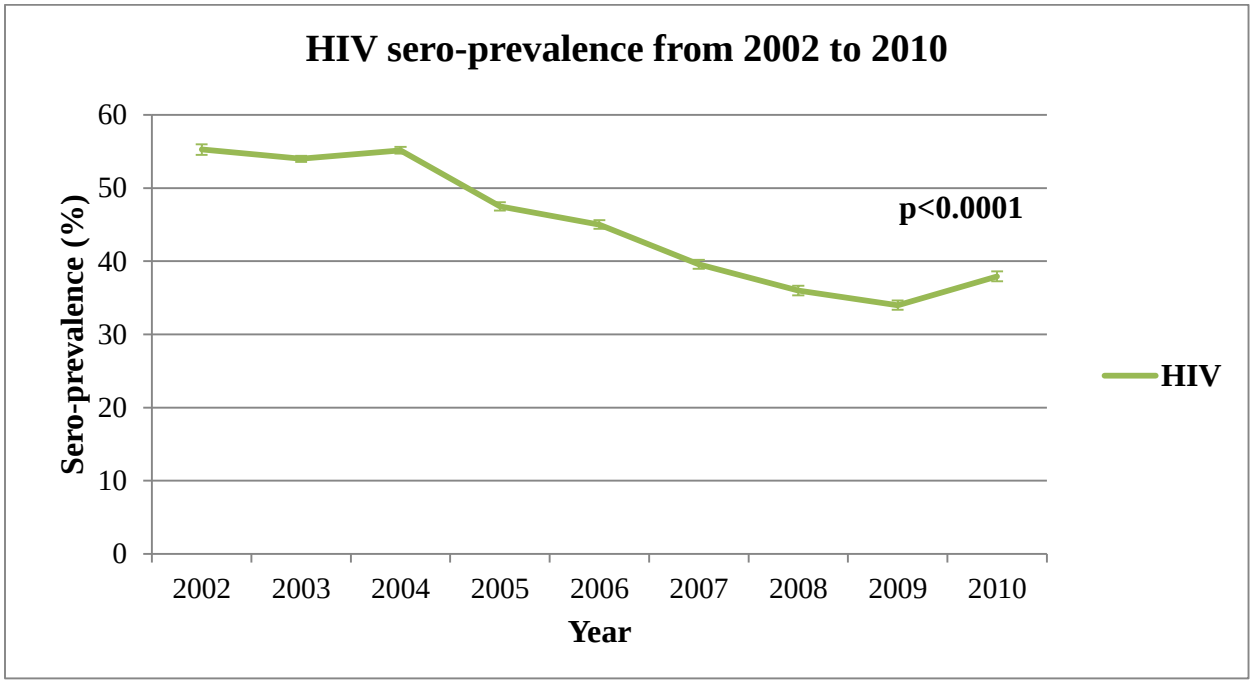

Figure 6: HIV sero- prevalence for the study population from 2002 to 2010

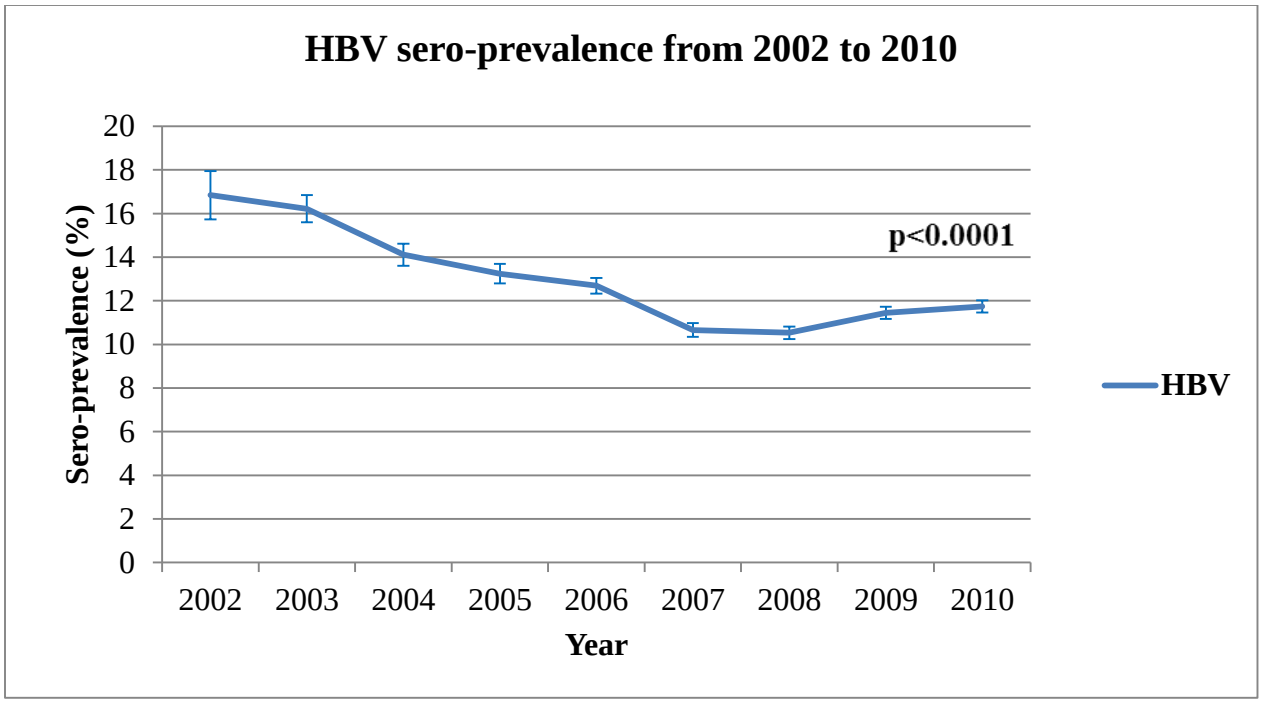

Figure 7: HBV sero–prevalence for the study population from 2002 to 2010

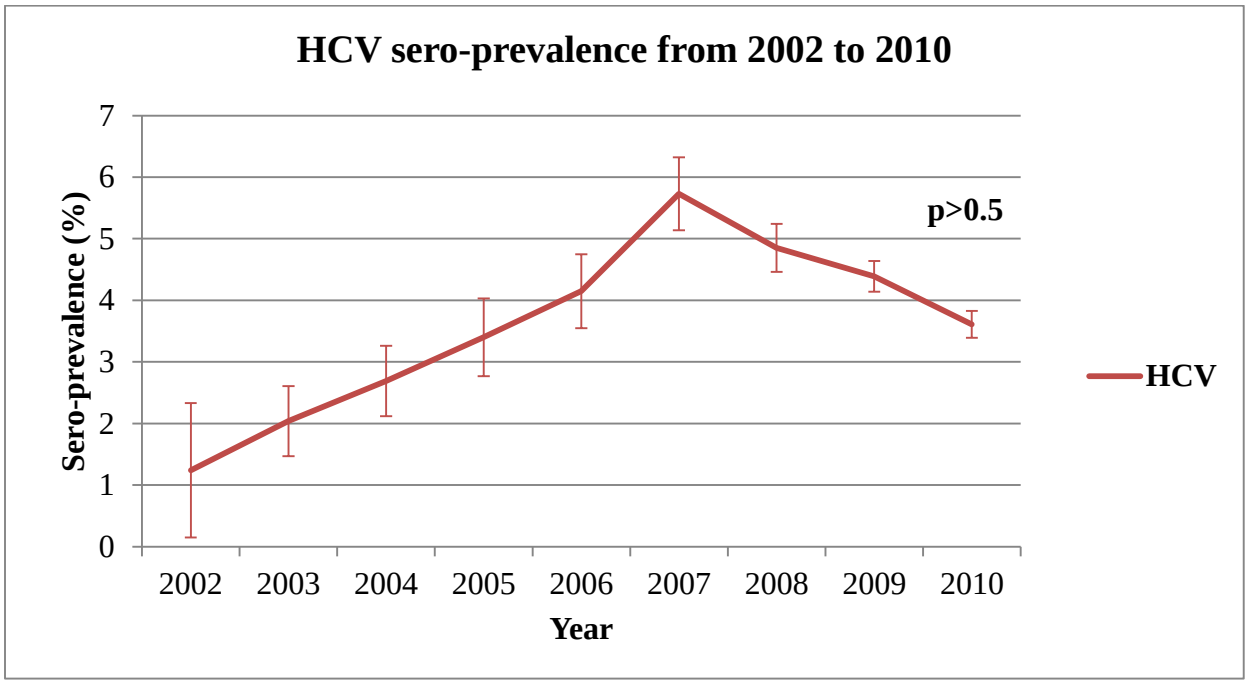

Figure 8: HCV sero-prevalence for the study population from 2002 to 2010

4.3.4 HIV/HBV, HIV/HCV and HBV/HCV co-infections

The odds of having markers for Hepatitis B or C infection was increased in HIV positive individuals (Table 5).

Those with HIV had 3.19 times the odds of being positive for HBsAg (OR = 3.19, 95% CI 2.95-3.44%, p<0.0001), and 2.06 times the odds of being HBeAg positive (OR = 2.06, 95% CI 1.76-2.40%, p<0.0001), than those without HIV (Table 5).

Conversely, those with HIV were less likely be positive for HBsAb (OR = 0.36, 95% CI 0.31-0.42%, p<0.0001) (Table 5).

Those with HIV infection had 2.91 times the odds of being HCV IgG positive (OR = 2.91, 95% CI 2.40-3.53%), than those without HIV (Table 5).

Of those individuals tested for HBsAg and HCV IgG, 15.76% were seropositive for both markers (Table 6). Those with HBV had 1.38 times the odds of being co-infected with HCV (OR = 1.38, 95% CI 1.25-1.53%), compared to those without HBV (Table 6).

Table 5: Comparison of hepatitis markers between HIV positive and HIV negative individuals, in the study population from 2002 to 2010

Hepatitis Marker*		Number	HIV negative	HIV positive	Odds Ratio (95% CI)	p-value
HBV						
	HBsAg positive (%)	54 097	3.40	10.10	3.19 (2.95-3.44)	p<0.0001
	HBsAb positive (%)	7148	72.96	49.47	0.36 (0.31-0.42)	p<0.0001
	HBeAg positive (%)	3055	25.16	40.89	2.06 (1.76-2.40)	p<0.0001
HCV						
	HCV IgG positive (%)	17 838	1.81	5.08	2.91 (2.40-3.53)	p<0.0001

(*Only among subjects who were tested for the respective marker. HBsAb considered positive when antibody titre >10 mIU/mL. HBsAb usually tested after administration of Hepatitis B vaccination. HBeAg only tested if HBsAg is positive.)

Table 6: Association between HBV and HCV sero-prevalence in the study population from 2002 to 2010

	HBV positive (%)	Odds Ratio (95% CI)	p-value
HCV negative	11.91		
HCV positive	15.76	1.38 (1.25 -1.53)	p<0.0001

4.4 SUMMARY

More females than males were tested, of the 507 834 individuals who had HIV, HBV or HCV tests. The majority of tests were from the eThekwini district. The overall sero-prevalence of HIV was 47.00%, 12.05% for HBV and 4.13% for HCV, for KZN from 2002 to 2010. The highest sero-prevalence for HIV, and HCV was in the 30-35 year age group, while for HBV it was in the 20-25 year age group. There was a relatively high sero-prevalence of HBV in the 0-1 year age group. HIV sero-prevalence was higher in females, while HBV and HCV sero-prevalence was higher in males. In terms of health districts, uThukela had the highest HIV sero-prevalence, while Amajuba and Zululand had the highest HBV and HCV sero-prevalence respectively. The overall sero-prevalence of HIV and HBV has decreased significantly over time ($p<0.0001$), while there was no significant change in the sero-prevalence of HCV ($p>0.5$).

Those with HIV had 3.19 times the odds of being positive for HBsAg (OR = 3.19, 95% CI 2.95-3.44%, $p<0.0001$), and 2.06 times the odds of being positive for HBeAg (OR = 2.06, 95% CI 1.76-2.40, $p<0.0001$) than those without HIV. Those with HIV were less likely to be positive for HBsAb (OR = 0.36, 95% CI 0.31-0.42%, $p<0.0001$).

Those with HIV had 2.91 times the odds of being positive for HCV IgG (OR = 2.91, 95% CI 2.40-3.53%, $p<0.0001$) compared to those without HIV. Those with HBV had a 1.38 times the odds of being co-infected with HCV (OR = 1.38, 95% CI 1.25-1.53%) compared to those without HIV.

5 CHAPTER V: DISCUSSION

5.1 INTRODUCTION

In this chapter, the sero-prevalence of HIV, HBV and HCV in terms of age, gender and KZN health district from 2002 to 2010 is discussed. The demonstrated associations between HIV and HBV, HIV and HCV, and HBV and HCV sero-prevalence are analysed.

The findings of the study are considered in relation to the possible biases and limitations of the study design, the data collection process and the results of the study. The generalisability of the study is also discussed.

5.2 FINDINGS

The format of the discussion is similar to that of the results.

5.2.1 The socio-demographic profile (age, gender, district of residence) of the study population

The demographic characteristics of this study population differ from other studies which have documented HIV and HBV/HCV co-infections.

Size

This study population is the largest population based study of HIV and HBV/HCV co-infections in KZN, and in South Africa (N = 507 834). The sample size of other observational studies conducted in South Africa are characterised by relatively smaller numbers (Table 2). Two studies which describe large sample sizes are those of Barth [5] and Madhava [42]. Barth performed a systematic review and meta-analysis of HIV and HBV/HCV co-infection in sub-Saharan countries, which reviewed results from 12 639 HIV/HBV and 9029 HIV/HCV co-infected individuals [5]. Madhava conducted a review of HCV infection in sub-Saharan countries, which included a review of 16 cohorts from South Africa, with a sample size of 68 931 individuals [42]. However, this review did not include HIV/HCV co-infections [42].

Age

In this study population, the majority of the HIV, HBV and HCV tests were conducted in the 25-30 and 35-40 year categories. The age range of the study population was broad (from newborn to 103 years). This is in contrast to previous studies (as shown in Table 2), in which the age range is limited by the choice of the study population, such as attendees of ARV or antenatal clinics.

Gender

More females than males were tested for HIV, HBV and HCV in this study population,. This is in keeping with several other studies (Table 2) [34, 64-67, 73]. The study by Burnett was conducted in antenatal clinics, and thus comprised entirely of pregnant females [66].

Health district

This study has analysed test results from all 11 KZN health districts. Similar coverage has not been attained in other studies (as shown in Table 2).

5.2.2 HIV, HBV and HCV sero-prevalence among the study population

The overall HIV sero-prevalence described in this study was 47% (95% CI 46.81-47.19%). This is higher than the sero-prevalence observed in the National Antenatal Surveys for KZN, which ranged from 37.5% (95% CI 35.2-39.8%) in 2002 to 39.5% (95% CI 38.0-41.0%) in 2010 [11, 81, 82]. A possible reason for the higher sero-prevalence in this study population is that the HIV tests were conducted on specimens from individuals who had clinical indications for the HIV tests. This is in contrast to the Antenatal Survey, where all consenting woman attending antenatal clinics are tested for HIV, whether or not a clinical indication exists.

The overall HBV sero-prevalence was 12.05% (95% CI 11.92-12.17%) in this study. Previous studies have documented a wide range in HBV sero-prevalence [23-25, 27-29] . This variation is dependent on a number of factors, such as when the studies were conducted (pre or post HBV vaccine inclusion into the EPI in South Africa; geographic, race and gender differences, the choice of the respective study populations, including high risk cohorts and the presence of co-infections, including HIV [23-25, 27-29].

The overall HCV sero-prevalence was 4.13% (95% CI 3.99-4.27%) in this study, which is higher than the mean HCV prevalence of 3.0% (range 0.0-40%) described in the study by Madhava [42]. A possible reason for the lower prevalence is that a number of the studies in the review, included results from HCV assays that were done on samples that had been stored for long periods of time [22]. The Madhava review included studies that were conducted relatively early in the HIV epidemic [42]. HCV sero-prevalence, like HBV, also differs depending on geography, race, gender, the inclusion of high risk populations, and the presence of co-infections, including HIV [42].

5.2.3 Sero-prevalence of HIV, HBV and HCV in terms of age, gender, health districts and time

Age

HIV sero-prevalence was highest (66.44%) in the 30-35 age category (Table 11, Appendix B) in this study population. This is similar to the findings from the 2007-2011 National Antenatal Surveys, where the highest HIV sero-prevalence is in the 30-34 year category [11, 82]. This may be a reflection of the epidemiology of the HIV epidemic in South Africa; those infected early on with HIV are surviving for longer periods [6].

HBV sero-prevalence was highest (15.74%) in the 20-25 age category (Table 12, Appendix B). This is in keeping with the findings by Kew, that HBV infection in South Africans is highest in the young and decreases with increasing age [30]. Studies have shown that patients in the 20-30 year age group were more likely to have evidence of HBV infection than older age groups [30, 83, 84]. This increase in prevalence could be associated with the onset of sexual activity and continued sexual transmission in this age group [30].

The relatively high sero-prevalence (9.45%) of HBV in the 0-1 year age category (Figure 2 and Table 12 in Appendix B) raises the possibility of ongoing perinatal or postnatal HBV transmission. The timing of exposure is of clinical importance since perinatal exposure is associated with a 90% risk of chronic Hepatitis B disease in the infant [20, 22]. However, this

finding is in contrast to a recent South African study which reported 1.2% (3/303) of children (5-24 months of age) being HBsAg positive [26].

HCV sero-prevalence, was highest (5.03%) in the 30-34 year group (Table 13, Appendix B) in this study. This is different to the findings of Madhava, who described median HCV prevalence as 1.3% (range 0.0%-11%), 3.0% (range 0.0-28%) and 12% (range 0.0%-55%) in the <20 year, 20-40, and >40 year age groups respectively [42]. The limitations of this study [42] were described in Chapter Two .

Gender

HIV sero-prevalence was higher in females when compared to males (47.81% vs 45.98%, $p < 0.0001$) (Table 14, in Appendix B) in this study. This is in keeping with the findings that females are more vulnerable to HIV acquisition than males which could be due to a number of factors, such as biological susceptibility (hormonal mechanisms, abnormal genital tract flora or vaginal infections), and factors influencing access to preventative and other health services [10].

HBV and HCV sero-prevalence was higher in males than in females (HBV: 15.54% vs. 9.91%, $p<0.0001$ and HCV: 4.38% vs. 3.8%, $p<0.0001$) (Table 14 in Appendix B) in this study. Other studies described HBV infection as being more common in South African males than females, with a mean ratio of 2.6:1.0: this is applicable to rural and urban settings, as well as to adults and children, despite both genders being equally exposed to HBV [28, 30, 85, 86].

A population based study of HCV prevalence in Egypt reported that females were more likely to have cleared HCV infection than males (44.6% v 33.7%, respectively; $p < .001$) resulting in spontaneous resolution [87]. A similar finding is seen with HBV infection, where viral clearance from blood is more common among females than males [88]. Possible reasons for the gender differences include the role of genetic or hormonal factors [87].

Health District

There was variation in HIV, HBV and HCV sero-prevalence across the 11 KZN districts in this study. The highest HIV sero-prevalence was in uThukela (87.27%), the highest HBV sero-prevalence was in Amajuba (38.94%), and Zululand had the highest HCV sero-prevalence (6.30%) (Figure 4 and Tables 21-23 in Appendix B).

The variation in HIV sero-prevalence among districts in this study is much greater than that observed in the previous National Antenatal Surveys [11, 81, 82]. This is most likely due to the relatively homogenous study population in the Antenatal Surveys.

There is also a variation in HBV and HCV sero-prevalence across the districts but there is no published data available for comparison. However, the difference in HBV prevalence in rural compared to urban areas is documented. In rural areas, chronic HBV infection is acquired early in life which is in contrast to urban areas, where HBV is generally acquired later in life [30].

Time

The sero-prevalence of HIV has decreased significantly over time (from 2002 to 2010) ($p< 0.0001$) (Figures 5 and 6). This finding may be due to the national rollout of ART in 2004 which greatly improved the uptake of HIV testing. Consequently an increasing number of individuals tested positive for HIV and commenced on ARVs. Because there were no further indications for formal HIV diagnostic testing, this may have contributed to observed decrease in HIV sero-prevalence noted in Figures 5 and 6 [89, 90].

A general decline in HBV sero-prevalence is noted over the study period ($p<0.0001$) (Figures 5 and 7) which may reflect the long term population benefits of HBV vaccination (introduced into the EPI in 1995) [22].

There was no significant change in the sero-prevalence of HCV (as reflected in the wide confidence intervals of each time point, and $p> 0.05$) (Figures 5 and 8).

It is considered important to study the sero-prevalence over time to address the criticism directed at studies which combine data from numerous time points without considering temporal changes in distribution or transmission [91].

5.2.4 HIV/HBV, HIV/HCV and HBV/HCV co-infections

The odds of having markers for Hepatitis B infection was increased in HIV positive individuals (Table 5).

Those with HIV infection had 3.19 times the odds of being positive for HBsAg (OR = 3.19, 95% CI 2.95-3.44%, p<0.0001) and 2.06 times the odds of being HBeAg positive (OR = 2.06, 95% CI 1.76-2.40%, p<0.0001) than those without HIV (Table 5). Existing studies have reported a wide variation in HIV/HBV co-infection prevalence, ranging from 0.4% [65] to 22.9% [67]. A systematic review and meta-analysis conducted by Barth demonstrated a RR of 1.40 (95% CI 1.16-1.69%) for having a positive HBsAg among HIV positive individuals, compared to those without HIV [5]. The systematic review did not show a significant difference in HBeAg prevalence between HIV positive and HIV negative individuals [5].

Those with HIV were less likely be positive for HBsAb (OR = 0.36, 95% CI 0.31-0.42%, p<0.0001) (Table 5). This may reflect the immunosuppressive effects of HIV which may eventually lead to the loss of protective antibodies against HBV infection [48]. This loss of protective immunity may result in HBV reactivation or exposure to new HIV infections [48].

Those with HIV infection had 2.91 times the odds of being HCV IgG positive (OR = 2.91, 95% CI 2.40-3.53%), than those without HIV (Table 5). The measures of association observed in other studies range from a RR of 1.60 (95% CI 1.05-2.45%) [5] to an OR of 8.8 (95% 5.4-14.3%), $p < 0.001$ [73], possibly reflecting differences in study population and design.

Of those individuals who were tested for HBsAg and HCV IgG, 15.76% were seropositive for both markers (Table 6). Those with HBV were found to have 1.38 times the odds of being co-infected with HCV (OR = 1.38, 95% CI 1.25-1.53%) compared to those without HBV. This in contrast to the studies conducted by Soni [43] and Kew [74] where the prevalence of HBV/HCV co-infection ranged from 0.91% to 8.66% respectively (as shown in Table 6).

5.3 VALIDITY

This section discusses the internal validity and the external validity (generalisability) of the study.

5.3.2 Internal validity

The only data source used was the LIS at the Inkosi Albert Luthuli Central Hospital, Department of Virology, National Health Laboratory Service. The Department of Virology is accredited by SANAS [75] and is the reference laboratory for KZN.

In the Department of Virology laboratory, specimens are routinely tested as soon as possible after being received in the laboratory. Repeated freezing and thawing of specimens are avoided, which reduces the possibility of erroneous results that may arise from such practices [78].

In accordance with standardized procedures, the demographic and clinical data contained on request forms accompanying specimens was captured into the LIS by laboratory data-capturers, using a standardized template. Patients were uniquely identified by a hospital number; specimens were uniquely identified by a bar-coded specimen number. The data was cross checked by staff to limit the possibility of internal transcription errors.

The assays done in the laboratory are highly sensitive and specific. The markers selected for the diagnosis of HIV, HBV, HCV are standard serological markers (Table 2). The results of this study were based on automated ELISAs which are regarded as gold standards in serological diagnosis [78, 79].

The results of laboratory tests for each patient were uploaded electronically into the database and were facilitated by an interface between the specimen analyser and the LIS, and were cross checked manually by laboratory staff. These measures minimize the possibility of erroneous results being entered into the LIS database.

5.3.3 External validity

The Department of Virology is the reference Virology laboratory for the public health sector in KZN, where the study was conducted. The laboratory received the majority of specimens for viral tests in KZN. Thus the results of this study are generalizable to individuals attending public health facilities in KZN who require a test for HIV, HBV or HCV.

This study is not generalisable to individuals attending private health care facilities, or to individuals who had no indication for the specific tests to be done, or to those who had indications for these tests but had point of care HIV or HBV tests at health facilities (fixed or mobile).

The generalisability of this study can be considered to be greater than those studies which used small cohorts in particular settings since this study reflects results from a wide geographic distribution across KZN and from all levels of public health facilities (including both inpatients and outpatients) and over a nine year time period.

5.4 BIAS AND LIMITATIONS

The bias and limitations of this study are discussed with regards to design, data collection and findings of the study.

The retrospective design of this study makes investigating the timing of infection difficult since it was not possible distinguish which infection occurred first: HIV or HBV or HCV infection. Also, a retrospective study does not exclude the possibility that individuals may have acute HBV and HCV infection.

Selection bias may be due to samples received for HIV testing, based on the presence of risk factors for HIV. However, since HBV and HCV share common risk factors with HIV, it is possible that the prevalence of HBV and HCV may be overestimated.

The study setting is the Department of Virology which is the accredited central referral laboratory in KZN [75]. However, there is one hospital that performs HIV serological tests in its own laboratory and does not send sera for testing to the Department of Virology at Inkosi Albert Luthuli Central Hospital. In addition, results from point of care tests done across KZN for HIV and HBsAg were not reflected in the database.

Information bias may be present as this study analysed only serological markers for HIV, HBV and HCV. The results of molecular tests, such as PCR, which are used to exclude false negative

results in the window period were not included. However, the presence of such bias is likely to be non-differential in nature, with the measure of association being biased towards the null.

5.5 SUMMARY

This study is the largest population based study of HIV and HBV/HCV co-infection in KZN and in South Africa (N = 507 834). The study documented the overall HIV, HBV and HCV sero-prevalence in KZN from 2002 to 2010. There were differences in HIV, HBV and HCV sero-prevalence for age, gender, health district and over time. There was a higher sero-prevalence for HIV and HCV, in the older age group (30-35 years), than for HBV (20-25 years). Also HIV sero-prevalence was higher in females than in males; in contrast to HBV and HCV. The 0-1 year age group had a relatively high HBV sero-prevalence. Variations in sero-prevalence for HIV, HBV and HCV was described in each of the 11 KZN health districts. There was a significant decrease in the sero-prevalence of HBV and HIV over time. Those with HIV had more than three times the odds of being positive for HBsAg and more than two times the odds of having HBeAg, compared to those without HIV. Those with HIV were also less likely to have evidence of protective antibodies against Hepatitis B. Those with HIV had almost three times the odds of having HCV IgG. Finally, those with HBV were 40% more likely to be co-infected with HCV.

6 CHAPTER VI: RECOMMENDATIONS AND CONCLUSIONS

6.1 INTRODUCTION

This study is the largest population based study of HIV and HBV/HCV co-infection in KZN and in South Africa (N = 507 834). The study demonstrated differences in HIV, HBV and HCV sero-prevalence for age, gender, health district and over time (2002 to 2010). There was a higher sero-prevalence for HIV and HCV, in the older age group (30-35 years) than for HBV (20-25 years). The 0-1 year age group had a relatively high HBV sero-prevalence. This study showed an increased odds of being sero-positive for HBV or HCV, in those with HIV (HBV: OR = 3.19 and HCV: OR = 2.91). Those with HIV were also less likely to have evidence of protective antibodies against Hepatitis B. Those with HBV had 1.38 times the odds of being positive for HCV, compared to those without HBV.

This chapter makes recommendations based on the findings of this study.

6.2 CONCLUSION

This study documented the high sero-prevalence of HIV, HBV and HCV over 9 years for KZN. This study demonstrated that a significant number of HIV positive individuals are co-infected with either HBV or HCV.

This finding is of clinical relevance since co-infected individuals have more severe hepatic disease and are at increased risk of side effects from ARVs.

This study adds to existing epidemiological data on HIV, HBV and HCV sero-prevalence and co-infection, in a South African setting. This data may be used to inform public health policy, particularly regarding screening and prevention of HBV and HCV.

6.3 RECOMMENDATIONS

High HBV sero-prevalence in the 0-1 year group

Measures to address the finding of a relatively high HBV sero-prevalence in the 0-1 year age group involve a comprehensive public health strategy, which includes vaccination, screening, monitoring and surveillance. In the South African EPI, babies receive the Hepatitis B vaccine at 6, 10 and 14 weeks of age, currently. The recommendation is for an additional Hepatitis B dose to be administered at birth (within 24 hours) as part of the EPI [22] in order to address the relatively high sero-prevalence observed in the 0-1 year age group. This is in keeping with WHO recommendations [92].

Further recommendations include the screening of pregnant women for Hepatitis B markers (HBsAg and HBsAb) and subsequent immunisation of new-borns born to mothers with Hepatitis B [22]. At present there is insufficient population level data about the perinatal transmission of HBV in South Africa and it is not standard practice to screen pregnant women for HBV.

Current Hepatitis B vaccination coverage in the EPI should be improved. Recommendations to improve Hepatitis B vaccine coverage include addressing programmatic challenges, improving monitoring and evaluation, as well as improving awareness of HBV among health care workers and health users. Community Care Givers, and Family Health Teams should ensure that Road to Health cards are completed and that vulnerable mothers and babies (including mothers without antenatal bookings and babies born at homes, and those in rural areas) should be linked to immunisation services and followed up accordingly [22].

Active surveillance should be expanded by conducting representative nationwide Hepatitis B sero-prevalence surveys in order to ascertain the long-term impact of Hepatitis B vaccination, as part of the EPI [37]. Notably, there is no locally available information on the long term effectiveness of the Hepatitis B vaccine in children [26].

High HBV sero-prevalence in the 20-25 year age group

In order to address the high HBV sero-prevalence observed in the 20-25 year age group, it is recommended that an adolescent Hepatitis B vaccine dose be added to the vaccination schedule for those with incomplete Hepatitis B vaccine records in their Road to Health cards [22]. This dose should be administered in schools, by nurses from school health teams. A similar model of vaccine delivery is being used for the national rollout of the Human Papillomavirus vaccination of female learners in schools in South Africa [93].

High sero-prevalence of HIV/HBV, HIV/HCV and HBV/HCV co-infections

Recommendations arising from the findings of high sero-prevalence of co-infections include screening and vaccination, prevention, early diagnosis and treatment, and linkage to services.

There should be screening of HIV positive individuals for HBV and HCV in ART programs, prior to initiation of ART. Those found to be co-infected with HIV/HBV should receive antiretroviral therapy which is also active against HBV. These patients also require careful follow up and management due to the potential for complications such as immune reconstitution, cirrhosis and hepatocellular carcinoma [39]. These patients should be advised that their household contacts and sexual partners are at increased risk for HBV and should be vaccinated, where appropriate [39]. Patients with HIV/HCV co-infection should also be monitored carefully for hepatic and renal complications [73, 94].

This study reinforces the need to screen for Hepatitis B infection in those with HIV, and the need to vaccinate HIV positive individuals, who screen negative for Hepatitis B, as recommended by the Southern African Clinicians Society [95]. HIV positive individuals do not respond optimally to the Hepatitis B vaccine and may require booster doses, and continued monitoring and follow up [95].

The high sero-prevalence of co-infections poses a risk to health care workers exposed to multiple viral infections that may be occupationally transmitted. It is therefore recommended that the National DOH increase the awareness, implementation, monitoring and evaluation of its screening policy for the prevention and control of HBV and HCV in health care workers [22, 96].

Health care workers should be required to submit proof of their HBV immunity prior to being employed and (HBV negative) health care workers who lack immunity should be vaccinated [22, 96]. This would be similar to the National Health System in United Kingdom which includes appropriate support, health education, counselling, provisions for post exposure prophylaxis and linkage to relevant health care services.[97].

Trends in the sero-prevalence of co-infection should be monitored on an ongoing basis. An example would be including hepatitis markers in the annual South African National Antenatal Surveys [11].

Variation in the sero-prevalence of HBV and HCV, by health district and time period

This study demonstrated variation in the sero-prevalence of HBV and HCV by health district and over time. It is likely that this variation will continue, due to the heterogeneity in the distribution of populations. This means that is important to have ongoing accurate district based estimates of disease burden due to Hepatitis B and C. In order to do this, the existing system of passive notification needs to be strengthened. Recommendations to address challenges with under diagnosis and under reporting involve: improving the reporting format, increasing dissemination of surveillance findings to health care workers educating health care workers and students regarding the importance of notification in monitoring and planning, as well as the need for accurate epidemiological data to inform public health policy [37, 38].

6.4 RECOMMENDATIONS FOR FURTHER STUDY

The high HBV sero-prevalence observed in the 0-1 year age group should be explored in large scale, representative prospective cohort studies, to confirm the study findings and to determine the underlying reasons for the high sero-prevalence.

The differences in sero-prevalence observed between districts and between different time periods should be studied using spatial modelling tools to identify geographic ‘hot spots’ or disease

clusters which may inform future targeted health interventions. Models should also be developed to predict future trends in the sero-prevalence of these viral infections, so that appropriate planning and resource allocation can be made for the future.

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8 APPENDIX

APPENDIX A

University of KwaZulu-Natal Biomedical Research Ethics Approval

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
Biomedical Research Ethics Administration
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29 June 2011

Dr. N Tathiah
Department of Public Health Medicine
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Tathiah

PROTOCOL: A retrospective study of Hepatitis A,B,C, and HIV in KwaZulu- Natal for the period 2002-2010:epidemiological and public health aspects. REF: BE038/11

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application dated 25 February 2011.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 15 June 2011 to queries raised on 19 April 2011 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 29 June 2011.

This approval is valid for one year from **29 June 2011.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics11415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **10 August 2011.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

University of KwaZulu-Natal Postgraduate Education Committee Approval

UNIVERSITY OF
KWAZULU-NATAL

7 June 2011

Professor CC Jinabhai
Department of Public Health Medicine
Nelson R Mandela School of Medicine

Dear Professor Jinabhai

PROTOCOL: "Epidemiology of Hepatitis A, B, C, and HIV in KwaZulu-Natal: 2002 to 2010."
Student: N Tathiah, student number: 941485264. (Department of Public Health Medicine)

The Postgraduate Education Committee ratified the approval of the abovementioned study on 7 June 2011.

Please note:

- The Postgraduate Education Committee must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

Professor M Adhikari
Dean's Assistant: MMed Programmes
Postgraduate Education and Research Committee

CC. Dr N Tathiah

Biomedical Research Ethics Committee
Westville Campus

Postgraduate Education Administration,
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UNIVERSITY OF KWAZULU-NATAL

NATIONAL HEALTH LABORATORY SERVICE

20 December 2010

Postgraduate Education Committee, NRMSM, UKZN
and
Biomedical Research Ethics Committee,UKZN

RE: A retrospective study of Hepatitis A, B, C, and HIV in KwaZulu-Natal for the Period 2002 – 2010: epidemiological and public health aspects

I hereby grant permission for Dr Nerisha Tathiah to conduct the study"A retrospective study of Hepatitis A, B, C, and HIV in KwaZulu-Natal for the period 2002 – 2010: epidemiological and public health aspects.", and to use the Department of Virology laboratory database for this purpose

Yours Sincerely

APPENDIX B

Table 7: Age distribution of the study population from 2002 to 2010

Characteristic	Years
N = 462 162 (excluding 45 672 individuals or 8.99% with missing age* data)	
Mean age (95% CI)	29.34 (29.30 – 29.39)
Median age	30.00
Standard Deviation	16.89
Range	0 – 103
Interquartile Range	20.00

(*age at which individual had first serological test for HIV, HBV or HCV recorded in the database)

Table 8: Age categories for individuals with HIV, HBV and HCV serological tests in the study population from 2002 to 2010

Age categories (year/s)	Number, %		HIV tests Number, %		HBV tests Number, %		HCV tests Number, %	
Newborn-1	42 869	9.28	24 116	9.87	12 668	5.19	4532	6.32
1-5	18 631	4.03	14 140	5.78	6513	2.67	1914	2.67
5-10	16 383	3.54	11 611	4.75	7347	3.01	2080	2.90
10-15	14 547	3.15	10 358	4.24	8025	3.29	2388	3.33
15-20	29 240	6.33	19 796	8.10	12 236	5.01	3678	5.13
20-25	55 455	12.00	31 536	12.90	25 757	10.55	7642	10.66
25-30	67 479	14.60	32 404	13.26	28 310	11.60	10 022	13.98
30-35	62 378	13.50	26 468	10.83	45 538	18.66	10 277	14.34
35-40	47 268	10.23	20 242	8.28	28 820	11.81	8065	11.25
40-45	34 496	7.46	15 951	6.53	20 941	8.58	5943	8.29
45-50	24 403	5.28	11 816	4.83	15 225	6.24	4704	6.56
50-55	17 914	3.88	9276	3.79	11 430	4.68	3544	4.94
55-60	13 433	2.91	7149	2.92	8992	3.68	2936	4.10
60-65	7885	1.71	4423	1.81	4385	1.80	1675	2.34

65-70	4957	1.07	2704	1.11	4482	1.84	1165	1.63
70-75	2668	0.58	1437	0.59	1877	0.77	624	0.87
75-80	1347	0.29	656	0.27	979	0.40	309	0.43
80-85	557	0.12	265	0.11	383	0.16	130	0.18
85-90	198	0.04	80	0.03	147	0.06	52	0.07
90-95	37	0.01	19	0.01	29	0.01	4	0.01
95-100	15	0	9	0	10	0	5	0.01
>100	3	0	3	0	0	0	0	0
Missing data (Those with no age data)	**45671**		**21952**		**22212**		**7527**	

Table 9: Gender distribution of individuals with HIV, HBV and HCV serological tests in the study population from 2002 to 2010

Gender	HIV tests Number, %		HBV tests Number, %		HCV tests Number, %	
Male	94895	35.62	89296	33.53	26920	33.99
Female	156745	58.84	148404	55.73	42659	53.86
Unknown gender	14771	5.540	28606	10.74	9637	7.320
Total	**266411**		**266306**		**79216**	

Table 10: Number and % of individuals with HIV, HBV or HCV serological tests in 11 KZN health districts for the study population from 2002 to 2010

District	HIV tests Number, %	HBV tests Number, %	HCV tests Number, %
Amajuba	1754 (0.66)	4058 (1.52)	920 (1.16)
eThekwini	178 521 (67.01)	17 786 (66.79)	44 264 (55.88)
Ugu	6373 (2.39)	2164 (0.81)	242 (0.31)
iLembe	3501 (1.31)	6742 (2.53)	1549 (1.96)
uMkhanyakude	1277 (0.48)	5887 (2.21)	1612 (2.03)
uMgungundlovu	4138 (1.55)	25 503 (9.58)	14 378 (18.15)
uThungulu	3808 (1.43)	5079 (1.91)	1103 (1.39)
Sisonke	3368 (1.26)	2384 (0.90)	586 (0.74)
uThukela	17 796 (6.68)	2848 (1.07)	534 (0.67)
uMzinyathi	762 (0.29)	3106 (1.17)	691 (0.87)
Zululand	883 (0.33)	1900 (0.71)	619 (0.78)
District not specified	44 229 (16.6)	28 770 (10.8)	12 718 (16.05)

Table 11: HIV results, by age categories for the study population from 2002 to 2010

	HIV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	1471 (6.1)	9452 (39.19)	13 193 (54.71)	24 116
1-5	359 (2.54)	8160 (57.71)	5621 (39.75)	14 140
5-10	238 (2.05)	7552 (65.04)	3821 (32.91)	11 611
10-15	132 (1.27)	8694 (83.94)	1532 (14.79)	10 358
15-20	243 (1.23)	12 924 (65.29)	6629 (33.49)	19 796
20-25	330 (1.05)	14 500 (45.98)	16 706 (52.97)	31 536
25-30	294 (0.91)	11 058 (34.13)	21 052 (64.97)	32 404
30-35	225 (0.85)	8653 (32.69)	17 590 (66.46)	26 468
35-40	160 (0.79)	8250 (40.76)	11 832 (58.45)	20 242
40-45	127 (0.8)	8148 (51.08)	7676 (48.12)	15 951
45-50	116 (0.98)	7214 (61.05)	4486 (37.97)	11 816
50-55	76 (0.82)	6455 (69.59)	2745 (29.59)	9276
55-60	75 (1.05)	5612 (78.50)	1462 (20.45)	7149
60-65	52 (1.18)	3811 (86.16)	560 (12.66)	4423
65-70	26 (0.96)	2448 (90.53)	230 (8.51)	2704
70-75	31 (2.16)	1300 (90.47)	106 (7.38)	1437
75-80	12 (1.83)	612 (93.29)	32 (4.88)	656
80-85	8 (3.02)	239 (90.19)	18 (6.79)	265

85-90	1 (1.25)	70 (87.5)	9 (11.25)	80
90-95	0 (0)	16 (84.21)	3 (15.79)	19
95-100	0 (0)	7 (77.78)	2 (22.22)	9
>100	1 (33.33)	0 (0)	2 (66.67)	3
Total	**3977**	**12 5175**	**11 5307**	**244 459**

Table 12: HBV results, by age categories for the study population from 2002 to 2010

	HBV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	1104 (8.71)	10 367 (81.84)	1197 (9.45)	12 668
1-5	520 (7.98)	5836 (89.61)	157 (2.41)	6513
5-10	372 (5.06)	6626 (90.19)	349 (4.75)	7347
10-15	163 (2.03)	7189 (89.58)	673 (8.39)	8025
15-20	155 (1.27)	10 179 (83.19)	1902 (15.54)	12 236
20-25	271 (1.05)	21 431 (83.20)	4055 (15.74)	25 757
25-30	294 (1.04)	23 798 (84.06)	4218 (14.9)	28 310
30-35	496 (1.09)	38 131 (83.73)	6911 (15.18)	45 538
35-40	254 (0.88)	24 675 (85.62)	3891 (13.5)	28 820
40-45	199 (0.95)	18 333 (87.55)	2409 (11.5)	20 941
45-50	148 (0.97)	13 645 (89.62)	1432 (9.41)	15 225
50-55	112 (0.98)	10 397 (90.96)	921 (8.06)	11 430
55-60	128 (1.42)	8283 (92.12)	581 (6.46)	8992
60-65	41 (0.94)	4098 (93.45)	246 (5.61)	4385
65-70	61 (1.36)	4201 (93.73)	220 (4.91)	4482
70-75	23 (1.23)	1776 (94.62)	78 (4.16)	1877
75-80	20 (2.04)	907 (92.65)	52 (5.31)	979
80-85	7 (1.83)	357 (93.21)	19 (4.96)	383
85-90	5 (3.4)	129 (87.76)	13 (8.84)	147
90-95	1 (3.45)	27 (93.1)	1 (3.45)	29
95-100	1 (10)	9 (90)	0 (0)	10
>100	0 (0)	0 (0)	0 (0)	0
Total	**4375**	**21 0394**	**29 325**	**244 094**

Table 13: HCV results, by age categories for the study population from 2002 to 2010

	HCV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	367 (8.1)	3984 (87.91)	181 (3.99)	4532
1-5	144 (7.52)	1713 (89.50)	57 (2.98)	1914
5-10	122 (5.87)	1894 (91.06)	64 (3.08)	2080
10-15	64 (2.68)	2284 (95.64)	40 (1.68)	2388
15-20	93 (2.53)	3502 (95.21)	83 (2.26)	3678
20-25	188 (2.46)	7210 (94.35)	244 (3.19)	7642
25-30	277 (2.76)	9268 (92.48)	477 (4.76)	10 022
30-35	302 (2.94)	9437 (91.83)	538 (5.23)	10 277
35-40	233 (2.89)	7426 (92.08)	406 (5.03)	8065
40-45	178 (3.00)	5482 (92.24)	283 (4.76)	5943
45-50	140 (2.98)	4366 (92.81)	198 (4.21)	4704
50-55	95 (2.68)	3304 (93.23)	145 (4.09)	3544
55-60	96 (3.27)	2728 (92.92)	112 (3.81)	2936
60-65	38 (2.27)	1555 (92.84)	82 (4.90)	1675
65-70	30 (2.58)	1075 (92.27)	60 (5.15)	1165
70-75	20 (3.21)	570 (91.35)	34 (5.45)	624
75-80	6 (1.94)	286 (92.56)	17 (5.50)	309
80-85	3 (2.31)	116 (89.23)	11 (8.46)	130
85-90	1 (1.92)	45 (86.54)	6 (11.54)	52
90-95	0 (0)	4 (100)	0 (0)	4
95-100	0 (0)	5 (100)	0 (0)	5
>100	0 (0)	0 (0)	0 (0)	0
Total	**2397**	**66 254**	**3038**	**71 689**

Table 14: HIV, HBsAg and HCV IgG results, by gender for the study population from 2002 to 2010

Test results	Female	Male	Unknown gender	Total
HIV				
Indeterminate (number, %)	2233(1.42)	1561(1.64)	552(3.74)	4346 (1.63)
95% CI	1.37-1.48	1.57-1.73	3.44-4.06	
p-value	p < 0.0001	p < 0.0001	p < 0.0001	
Negative (number, %)	79 578(50.77)	49 704(52.38)	7568(51.24)	136 850 (51.37)
95% CI	50.52-51.02	52.06-52.70	50.43-52.04	
p-value	p < 0.0001	p < 0.0001	p<0.0027	
Positive (number, %)	74 934(47.81)	43 630(45.98)	6651(45.03)	125 215 (47.00)
95% CI	47.56- 48.05	45.66-46.29	44.22-45.83	
p-value	p < 0.0001	p < 0.0001	p < 0.0001	
Total (number, %)	**156 745 (58.84%)**	**94 895 (35.62%)**	**14 771 (5.54%)**	**266 411**
HBsAg				
Indeterminate (number, %)	2377(1.60)	1685(1.89)	743(2.60)	4805(1.80)
95% CI	1.54-1.67	1.80-1.98	2.42-2.79	
p-value	p < 0.0001	p < 0.0001	p < 0.0001	
Negative (number, %)	131 325 (88.49)	73 736 (82.57)	24 360 (85.16)	229 421 (86.15)
95% CI	88.33- 88.65	82.32- 82.82	84.74- 85.57	

p-value	p < 0.0001	p < 0.0001	p < 0.0001	
Positive (number, %)	14 704(9.91)	13 875(15.54)	3503(12.25)	32 080 (12.05)
95% CI	9.76-10.06	15.30-15.78	11.87-12.63	
p-value	p < 0.0001	p < 0.0001	p < 0.0001	
Total (number, %)	**148 404 (55.73%)**	**89 296 (33.53)**	**28 606 (10.74)**	**266 306**
HCV IgG				
Indeterminate (number, %)	1305(3.06)	954(3.54)	303(3.14)	2562(3.23)
95% CI	2.90-3.22	3.32-3.76	2.80-3.59	
p-value	p < 0.0001	p < 0.0001	p < 0.0001	
Negative (number, %)	39 732 (93.14)	24 787 (92.08)	8865(91.99)	73 384 (92.64)
95% CI	92.89 – 93.38	91.75 – 92.40	91.43 – 92.52	
p-value	p < 0.0001	p < 0.0001	p < 0.0001	
Positive (number, %)	1622(3.80)	1179(4.38)	469(4.87)	3270(4.13)
95% CI	3.62-3.99	4.14-4.63	4.45-5.32	
p-value	p < 0.0001	p < 0.0001	p < 0.0001	
Total (number, %)	**42 659 (53.85)**	**26 920 (33.98)**	**9637 (12.17)**	**79 216**

Table 15: HIV results, by female gender and age categories for the study population from 2002 to 2010

Female gender	HIV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	623 (5.85)	4107 (38.56)	5920 (55.59)	10 650
1-5	197 (2.54)	4876 (62.84)	2687 (34.63)	7760
5-10	134 (1.92)	5019 (72.09)	1809 (25.98)	6962
10-15	97 (1.23)	6770 (86.18)	989 (12.59)	7856
15-20	188 (1.24)	9379 (61.64)	5650 (37.13)	15 217
20-25	213 (0.98)	8818 (40.58)	12 701 (58.44)	21 732
25-30	168 (0.83)	6174 (30.34)	14 005 (68.83)	20 347
30-35	121 (0.79)	4978 (32.53)	10 205 (66.68)	15 304
35-40	85 (0.74)	4881 (42.25)	6586 (57.01)	11 552
40-45	57 (0.65)	4606 (52.47)	4115 (46.88)	8778
45-50	60 (0.98)	3748 (61.11)	2325 (37.91)	6133
50-55	39 (0.83)	3290 (69.91)	1377 (29.26)	4706
55-60	31 (0.87)	2810 (78.80)	725 (20.33)	3566
60-65	24 (1.13)	1820 (85.93)	274 (12.94)	2118
65-70	11 (0.79)	1268 (91.29)	110 (7.92)	1389
70-75	14 (1.82)	705 (91.56)	51 (6.62)	770
75-80	8 (2.06)	363 (93.56)	17 (4.38)	388
80-85	6 (4.17)	129 (89.58)	9 (6.25)	144
85-90	1 (2.08)	42 (87.5)	5 (10.42)	48
90-95	0 (0)	6 (85.71)	1 (14.29)	7
95-100	0 (0)	3 (75)	1 (25)	4
>100	0 (0)	0 (0)	2 (100)	2
	2077	**73 792**	**69 564**	**145 433**

Table 16: HIV results, by male gender and age categories for the study population from 2002 to 2010

Male gender	HIV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	623 (5.71)	4068 (37.3)	6216 (56.99)	10 907
1-5	128 (2.25)	2884 (50.69)	2678 (47.07)	5690
5-10	80 (1.96)	2199 (53.79)	1809 (44.25)	4088
10-15	27 (1.34)	1552 (76.83)	441 (21.83)	2020
15-20	35 (0.96)	2955 (81.23)	648 (17.81)	3638
20-25	75 (0.91)	4918 (59.98)	3206 (39.10)	8199
25-30	99 (0.94)	4321 (40.89)	6148 (58.18)	10 568
30-35	78 (0.79)	3272 (33.11)	6533 (66.10)	9883
35-40	56 (0.72)	3047 (39.01)	4707 (60.27)	7810
40-45	53 (0.82)	3233 (49.98)	3182 (49.20)	6468
45-50	42 (0.82)	3179 (61.85	1919 (37.33)	5140
50-55	29 (0.69)	2969 (70.32)	1224 (28.99)	4222
55-60	36 (1.08)	2634 (79.34)	650 (19.58)	3320
60-65	23 (1.08)	1870 (87.75)	238 (11.17)	2131
65-70	12 (0.99)	1105 (90.72)	101 (8.29)	1218
70-75	15 (2.45)	549 (89.85)	47 (7.69)	611
75-80	3 (1.21)	230 (92.74)	15 (6.05)	248
80-85	2 (1.79)	103 (91.96)	7 (6.25)	112
85-90	0 (0)	24 (85.71)	4 (14.29)	28
90-95	0 (0)	9 (90)	1 (10)	10
95-100	0 (0)	4 (80)	1 (20)	5
>100	0 (0)	0 (0)	0 (0)	0
Total	**1416**	**45 125**	**39 775**	**86 316**

Table 17: HBV results, by female gender and age categories for the study population from 2002 to 2010

Female gender	HBV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	423 (8.91)	3977 (83.76)	348 (7.33)	4748
1-5	306 (8.72)	3123 (89.03)	79 (2.25)	3508
5-10	198 (4.86)	3730 (91.51)	148 (3.63)	4076
10-15	106 (2.03)	4818 (92.37)	292 (5.60)	5216
15-20	108 (1.25	7466 (86.19)	1088 (12.56)	8662
20-25	189 (1.06)	15 177 (85.51)	2382 (13.42)	17 748
25-30	167 (0.93)	15 549 (86.66)	2226 (12.41)	17 942
30-35	257 (1.01)	22 045 (86.98)	3044 (12.01)	25 346
35-40	117 (0.79)	13 240 (89.06)	1510 (10.16)	14 867
40-45	94 (0.88)	9680 (90.58)	913 (8.54)	10 687
45-50	76 (1.00)	6995 (92.04)	529 (6.96)	7600
50-55	44 (0.78)	5250 (92.82)	362 (6.40)	5656
55-60	62 (1.40)	4113 (93.14)	241 (5.46)	4416
60-65	17 (0.84)	1890 (93.75)	109 (5.41)	2016
65-70	33 (1.49)	2085 (93.96)	101 (4.55)	2219
70-75	10 (1.00)	938 (93.99)	50 (5.01)	998
75-80	15 (2.71)	507 (91.52)	32 (5.78)	554
80-85	6 (2.80)	198 (92.52)	10 (4.67)	214
85-90	3 (3.57)	73 (86.90)	8 (9.52)	84
90-95	0 (0)	14 (100)	0 (0)	14
95-100	0 (0)	4 (100)	0 (0)	4
>100	0 (0)	0 (0)	0 (0)	0
Total	**2231**	**120 872**	**13 472**	**136 575**

Table 18: HBV results, by male gender and age categories for the study population from 2002 to 2010

Male gender	HBV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	452 (11.06)	3261 (79.77)	375 (9.17)	4088
1-5	169 (6.8)	2249 (90.50)	67 (2.70)	2485
5-10	142 (5.26)	2374 (87.96)	183 (6.78)	2699
10-15	44 (1.97)	1846 (82.74)	341 (15.28)	2231
15-20	35 (1.37)	1864 (72.87)	659 (25.76)	2558
20-25	53 (1.01)	3928 (74.95)	1260 (24.04)	5241
25-30	89 (1.22)	5675 (77.78)	1532 (21.00)	7296
30-35	175 (1.17)	11 712 (78.04)	31 21 (20.80)	15 008
35-40	101 (0.94)	8716 (80.97)	19 47 (18.09)	10 764
40-45	83 (1.01)	6828 (83.42)	1274 (15.57)	8185
45-50	54 (0.87)	5354 (86.70)	767 (12.42)	6175
50-55	60 (1.24)	4325 (89.03)	473 (9.74)	4858
55-60	55 (1.41)	3555 (91.20)	288 (7.39)	3898
60-65	19 (0.90)	1972 (93.64)	115 (5.46)	2106
65-70	23 (1.17)	1843 (93.65)	102 (5.18)	1968
70-75	9 (1.19)	725 (95.65)	24 (3.17)	758
75-80	4 (1.07)	355 (94.67)	16 (4.27)	375
80-85	1 (0.65)	145 (94.16)	8 (5.19)	154
85-90	1 (1.89)	48 (90.57)	4 (7.55)	53
90-95	1 (7.14)	12 (85.71)	1 (7.14)	14
95-100	1 (25.00)	3 (75.00)	0 (0)	4
>100	0	0	0	0
Total	**1571**	**66 790**	**12 557**	**80 918**

Table 19: HCV results, by female gender and age categories for the study population from 2002 to 2010

Female gender	HCV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	137 (8.97)	1335 (87.37)	56 (3.66)	1528
1-5	53 (7.33)	639 (88.38)	31 (4.29)	723
5-10	46 (5.97)	689 (89.36)	36 (4.67)	771
10-15	33 (4.37)	706 (93.39)	17 (2.25)	756
15-20	27 (3.00)	852 (94.56)	22 (2.44)	901
20-25	53 (3.04)	1642 (94.26)	47 (2.7))	1742
25-30	76 (2.68)	2640 (93.19)	117 (4.13)	2833
30-35	112 (3.13)	3281 (91.70)	185 (5.17)	3578
35-40	97 (3.06)	2918 (92.08)	154 (4.86)	3169
40-45	72 (3.14)	2089 (91.18)	130 (5.67)	2291
45-50	55 (3.03)	1669 (91.96)	91 (5.01)	1815
50-55	31 (2.36)	1220 (92.71)	65 (4.94)	1316
55-60	43 (3.88)	1022 (92.32)	42 (3.79)	1107
60-65	19 (2.57)	681 (92.15)	39 (5.28)	739
65-70	10 (2.26)	410 (92.55)	23 (5.19)	443
70-75	10 (4.18)	221 (92.47)	8 (3.35)	239
75-80	2 (1.90)	99 (94.29)	4 (3.81)	105
80-85	2 (4.08)	44 (89.80)	3 (6.12)	49
85-90	1 (5.26)	16 (84.21)	2 (10.53)	19
90-95	0 (0)	2 (100)	0 (0)	2
95-100	0 (0)	2 (100)	0 (0)	2
>100	0 (0)	0 (0)	0 (0)	0
Total	**1238**	**36 072**	**1510**	**38 820**

Table 20: HCV results, by male gender and age categories for the study population from 2002 to 2010

Male gender	HCV results			
Age categories (year/s)	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Newborn-1	72 (5.70)	1136 (89.87)	56 (4.43)	1264
1-5	16 (7.17)	200 (89.69)	7 (3.14)	223
5-10	9 (4.17)	202 (93.52)	5 (2.31)	216
10-15	3 (1.41)	205 (96.24)	5 (2.35)	213
15-20	8 (2.40)	320 (95.81)	6 (1.8)	334
20-25	21 (2.35)	838 (93.63)	36 (4.02)	895
25-30	36 (2.89)	1133 (90.86)	78 (6.26)	1247
30-35	43 (3.18)	1222 (90.25)	89 (6.57)	1354
35-40	31 (3.13)	906 (91.61)	52 (5.26)	989
40-45	14 (2.24)	572 (91.52)	39 (6.24)	625
45-50	16 (3.32)	438 (90.87)	28 (5.81)	482
50-55	5 (1.61)	287 (92.28)	19 (6.11)	311
55-60	2 (0.76)	247 (93.92)	14 (5.32)	263
60-65	2 (1.46)	123 (89.78)	12 (8.76)	137
65-70	1 (0.98)	96 (94.12)	5 (4.90)	102
70-75	1 (1.85)	51 (94.44)	2 (3.70)	54
75-80	0 (0)	19 (90.48)	2 (9.52)	21
80-85	0 (0)	5 (100.00)	0 (0)	5
85-90	0 (0)	3 (75.00)	1 (25.00)	4
90-95	0 (0)	0 (0)	0 (0)	0
95-100	0 (0)	2 (100)	0 (0)	2
>100	0 (0)	0 (0)	0 (0)	0
Total	**879**	**22 177**	**1072**	**24 128**

Table 21: HIV results, by health district for the study population from 2002 to 2010

	HIV results			
District	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Amajuba	64 (3.65)	862 (49.14)	828 (47.21)	1754
eThekwini	2803 (1.57)	92 617 (51.88)	83 101 (46.55)	178 521
Ugu	49 (0.77)	2166 (33.98)	4159 (65.25)	6374
iLembe	101 (2.88)	1867 (53.33)	1533 (43.79)	3501
uMkhanyakude	40 (3.13)	672 (52.62)	565 (44.24)	1277
uMgungundlovu	314 (7.59)	2148 (51.91)	1676 (40.50)	4138
uThungulu	91 (2.39)	1678 (44.07)	2039 (53.55)	3808
Sisonke	48 (1.43)	1471 (43.68)	1849 (54.90)	3368
uThukela	228 (1.28)	2037 (11.45)	15 531 (87.27)	17 796
uMzinyathi	28 (3.67)	392 (51.44)	342 (44.88)	762
Zululand	25 (2.83)	494 (55.95)	364 (41.22)	883
District not specified	555 (1.25)	30 446 (68.84)	13 228 (29.91)	44 229
Total	**4346 (1.63)**	**136 850 (51.37)**	**125 215 (47.00)**	**266 411**

Table 22: HBsAg results, by district for the study population from 2002 to 2010

	HBsAg results			
District	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Amajuba	131 (3.23)	2347 (57.84)	1580 (38.94)	4058
eThekwini	2915 (1.64)	158 184 (88.93)	16 766 (9.43)	177 865
Ugu	30 (1.39)	1647 (76.11)	487 (22.50)	2164
iLembe	212 (3.14)	5424 (80.45)	1106 (16.40)	6742
uMkhanyakude	173 (2.94)	3720 (63.19)	1994 (33.87)	5887
uMgungundlovu	505 (1.98)	20 740 (81.32)	4258 (16.70)	25 503
uThungulu	99 (1.95)	3720 (73.24)	1260 (24.81)	5079
Sisonke	34 (1.43)	1970 (82.63)	380 (15.94)	2384
uThukela	62 (2.18)	2026 (71.14)	760 (26.29)	2848
uMzinyathi	56 (1.80)	2343 (75.43)	707 (22.76)	3106
Zululand	20 (1.05)	972 (51.16)	908 (47.79)	1900
District not specified	568 (1.97)	26 328 (91.51)	874 (6.51)	28 770

Total	**4805 (1.8)**	**229 421 (86.15)**	**32 080 (12.05)**	**255 306**

Table 23: HCV IgG results, by district for the study population from 2002 to 2010

	HCV IgG results			
District	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
Amajuba	39 (4.24)	841 (91.41)	40 (4.35)	920
eThekwini	1483 (3.35)	41 006 (94.64)	1775 (4.01)	44 264
Ugu	23 (9.5)	211 (87.19)	8 (3.31)	242
iLembe	57 (3.68)	1439 (92.90)	53 (3.42)	1549
uMkhanyakude	66 (4.09)	1458 (90.45)	88 (5.46)	1612
uMgungundlovu	450 (3.13)	13 078 (90.96)	850 (5.91)	14 378
uThungulu	49 (4.44)	1003 (90.93)	51 (4.62)	1103
Sisonke	19 (3.24)	533 (90.96)	34 (5.80)	586
uThukela	20 (3.75)	494 (92.51)	20 (3.75)	534
uMzinyathi	32 (4.63)	627 (90.74)	32 (4.63)	691
Zululand	16 (2.58)	564 (91.11)	39 (6.30)	619
District not specified	308 (2.42)	12 130 (93.38)	280 (2.20)	2718
Total	**2562 (3.23)**	**73 384 (92.64)**	**3270 (4.13)**	**79 216**

Table 24: HIV results for the study population, from 2002 to 2010

	HIV results			
Year	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
2002	181 (0.95)	8316 (43.79)	10 493 (55.26)	18 990
2003	485 (0.86)	25 598 (45.16)	30 605 (53.99)	56 688
2004	294 (0.64)	20 225 (44.21)	25 233 (55.15)	45 752
2005	255 (0.85)	15 447 (51.64)	14 210 (47.51)	29 912
2006	416 (1.56)	14 234 (53.42)	11 996 (45.02)	26 646
2007	631 (2.65)	13 770 (57.76)	9439 (39.59)	23 840
2008	724 (3.45)	12 708 (60.55)	7555 (36.00)	20 987
2009	716 (3.28)	13 676 (62.73)	7411 (33.99)	21 803
2010	500 (2.54)	11 739 (59.54)	7476 (37.92)	19 715
Total	**4202**	**135 713**	**124 418**	**264 333**

Table 25: HBV results for the study population, from 2002 to 2010

	HBV results			
Year	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
2002	101 (2.37)	3450 (80.80)	719 (16.84)	4270
2003	160 (1.23)	10 782 (82.55)	2119 (16.22)	13 061
2004	200 (1.12)	15 164 (84.77)	2524 (14.11)	17 888
2005	282 (1.28)	18 865 (85.49)	2921 (13.24)	22 068
2006	515 (1.6)	27 530 (85.71)	4076 (12.69)	32 121
2007	729 (2.09)	30 425 (87.25)	3718 (10.66)	34 872
2008	985 (2.2)	39 054 (87.27)	4712 (10.53)	44 751
2009	1236 (2.54)	41 867 (86.01)	5575 (11.45)	48 678
2010	597 (1.23)	42 270 (87.03)	5704 (11.74)	48 571
Total	4805	22 9407	32 068	266 280

Table 26: HCV results for the study population, from 2002 to 2010

	HCV results			
Year	**Indeterminate (Number, %)**	**Negative (Number, %)**	**Positive (Number, %)**	**Total**
2002	62 (38.51)	97 (60.25)	2 (1.24)	161
2003	328 (16.33)	1639 (81.62)	41 (2.04)	2008
2004	249 (9.05)	2429 (88.26)	74 (2.69)	2752
2005	105 (3.64)	2680 (92.96)	98 (3.40)	2883
2006	101 (2.49)	3784 (93.36)	168 (4.15)	4053
2007	119 (2.10)	5232 (92.18)	325 (5.73)	5676
2008	308 (2.81)	10 106 (92.33)	531 (4.85)	10 945
2009	770 (3.01)	23 656 (92.60)	1121 (4.39)	25 547
2010	520 (2.06)	23 755 (94.32)	910 (3.61)	25185
Total	**2562**	**73 378**	**3270**	**79 210**