

**SERO-PREVALENCE AND RISK FACTORS OF HEPATITIS B AND C VIRAL
INFECTION IN HIV INFECTED CHILDREN SEEN AT THE UNIVERSITY
TEACHING HOSPITAL, DEPARTMENT OF PAEDIATRICS AND CHILD
HEALTH, LUSAKA, ZAMBIA**

By

DR CHIMIKA PHIRI

(BScHb, MBChB)

**A dissertation submitted in partial fulfilment of the requirement for the award of the
degree of Master of Medicine in Paediatrics and Child Health**

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DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or any other University

Candidate.....

DR CHIMIKA PHIRI

(BScHB, MBChB)

Supervisor.....

DR SYLVESTER SINYANGWE

(BScHB, MBChB, MPCH, MPH, DTM&H, DIP.LAW, MMED PAEDS AND CHILD HEALTH)

UNZA LECTURER & CONSULTANT PAEDIATRICIAN

Department of Paediatrics and Child Health

Supervisor.....

DR EVANS MWILA MPABALWANI

(BScHB, MBChB, MSc, MMED PAEDS AND CHILD HEALTH)

CONSULTANT PAEDIATRICIAN

Department of Paediatrics and Child Health

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APPROVAL

The University of Zambia approves the dissertation of Dr Chimika Phiri as partial fulfilment of the requirement for the award of the degree of Master of Medicine in Paediatrics and Child Health.

Examiner 1

Name

Signed

Date

Examiner 2

Name

Signed

Date

Examiner 3

Name

Signed

Date

ABSTRACT

Title: Sero-prevalence and risk factors of Hepatitis B and C viral infection in HIV positive children seen at the Paediatric Centre of Excellence, University Teaching Hospital, Lusaka, Zambia

Background: Hepatitis B virus (HBV), Hepatitis C virus (HCV) and HIV are well reported in numerous studies from Europe and America, but there are few data on the prevalence of co-infection in African populations including Zambia.

Methods: In this cross-section study, we screened HIV positive children for Hepatitis B surface Antigen (HBsAg) and Hepatitis C antibody (HCV) seen at the University Teaching Hospital (UTH), Paediatric Centre Of Excellence(PCOE). Basic demographic data, Medical history and laboratory data were collected to determine possible risk factors to viral Hepatitis disease and HIV co-infection

Results: A total of 187 participants were recruited over a period of six months, from August 2014 to January 2015. There were 98 males (52.4%) and 89 females (47.6%). The median age was 9 years (IQR 1.7, 15). Out of all the children recruited, 126 children had received the three required doses of Viral Hepatitis B vaccines according to our national protocol. Overall, 5.9% (11/187) of the analyzed blood samples had HBsAg positive results and 0.5% (1/187) had HCV antibody positive. Among those that had received HBV vaccine, 4.7% (6/128) tested positive to HepBsAg test and 8.5% (5/59) of the non-immunized had HBV infection. After logistic regression, only AST serum level was associated with Hepatitis B Viral infection. However in clinical practice the AST levels were not significant since they were within normal ranges. The Viral Hepatitis infections were not associated with any history of Blood transfusion, scarification, or sexual history.

Conclusion: HBV infection in HIV infected children seen at PCOE is common at 5.9%, which falls in medium endemic area and HCV infection is low at 0.5% prevalence.

DEDICATION

I dedicate this study to my lovely wife, Mayaba and my children for their unwavering support during the period of the study.

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LIST OF ACRONYMS AND ABBREVIATIONS

ART	Antiretroviral therapy
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CD4+	T-lymphocyte bearing CD4 receptors
CHB	Chronic hepatitis B
CI	Confidence interval
CIDRZ	Centre for Infectious Disease Research in Zambia
DAA	Direct acting antiviral
DNA	Deoxyribonucleic acid
EVR	Early virology response
HAART	Highly active antiretroviral therapy
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN-α	Interferone – α
IgM	Immunoglobulin M
IL-2	Interleukin-2
OR	Odds ratio
PEG	Pegylated
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism
USA	United States of America
UTH	University Teaching Hospital
WHO	World Health Organisation
ZNBTS	Zambia National Blood Transfusion services

CHAPTER ONE

1.0 Background

Hepatitis is an inflammation of the liver, most commonly caused by a viral infection. There are five main hepatitis viruses, referred to as types A, B, C, D and E. These five types are of greatest concern because of the disease burden and death they cause and the potential for outbreaks and epidemic spread. In particular, viral Hepatitis types B and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis and cancer [1].

Worldwide, an estimated two billion people have been infected with the hepatitis B virus and more than 240 million have chronic liver infections. About 600 000 people die every year due to the acute or chronic consequences of hepatitis B [1]. Hepatitis C has estimated world prevalence of 3%, affecting nearly 170 million individuals worldwide [2].

Sub-Saharan Africa falls in medium to high endemic area for Hepatitis B infection [3]. In these areas, about 70 to 90% of the population becomes HBV infected before the age of 40 years and 5 to 20 % of people are HBV carriers [4]

In Zambia, Blood Bank data indicates that approximately 10% of healthy adult blood donors have chronic infection of Hepatitis B Virus (HBV) [5]. On the other hand the prevalence of Hepatitis C virus (HCV) is less than 1% among the healthy adult blood donors [5]. Hepatitis B surface Antigen (HBsAg) positive rate in Zambia is between 4-15% in pregnant mothers [5]. This means Zambia is in medium to high endemic area of hepatitis B. It also suggests that vertical transmission may not be a main route of Hepatitis B transmission in Zambia. Among hospitalised children the Hepatitis B carrier rate is 6.2%, and the prevalence of HBV infection is significantly higher in HIV antibody positive hospitalised children [5]. A study in Zambia among adults showed that Hepatitis B and C were common among HIV infected adults receiving Anti-Retroviral Therapy (ART) [6].

The likelihood that infection with the Hepatitis B virus becomes chronic depends upon the age at which a person becomes infected. Young children who become infected with the hepatitis B virus are most likely to develop chronic infections:

- 90% of infants infected during the first year of life develop chronic infections

- 30–50% of children infected between one to four years of age develop chronic infections

In adults:

- 25% of adults who become chronically infected during childhood die from hepatitis B-related liver cancer or cirrhosis
- 90% of healthy adults who are infected with the hepatitis B virus will recover and be completely rid of the virus within six months [1].

A vaccine against Hepatitis B has been available since 1982. Hepatitis B vaccine is 95% effective in preventing infection and its chronic consequences, and is the first vaccine against a major human cancer [1].

In developing countries, common modes of transmission are [1]:

- Perinatal (from mother to baby at birth)
- Early childhood infections (inapparent infection through close interpersonal contact with infected household contacts)
- Unsafe injection practices
- Unsafe blood transfusions
- Unprotected sexual contact

In many developed countries, Western Europe and North America, patterns of transmission are different from those in developing countries. The majority of infections in developed countries are transmitted during young adulthood by sexual activity and injecting drug use. Hepatitis B is a major infectious occupational hazard of health workers in these countries.

1.1 Statement of the problem

Although rates of co-infection with at least two of hepatitis B virus HBV, HCV and Human Immunodeficiency Virus (HIV) are well reported in numerous studies from Europe and America, there are few data on the prevalence of co-infection in African populations including Zambia.

Recent Studies have shown that there is relatively high liver-related mortality in HIV/HBV co-infection due to the accelerated course of hepatitis B in HIV-seropositive patients [64]. Persistent HBeAg reactivity and persistent high levels of HBV DNA have been associated with an increased progression of hepatitis B in HIV co-infected persons [64].

It has been demonstrated that lamivudine resistance occurs in more than 90% of HIV-HBV co-infected patients exposed to lamivudine for more than 4 years [33]. In Zambia, the current recommended first line ART for children less than 12 years contain Lamivudine. In addition, although the Zambia HIV national policy recommends pre-ART screening for HBV in all HIV infected patients, this is not routinely done in many centres.

1.2 Study justification

Currently the prevalence of HBV and HCV in HIV infected children in Zambia is not known. The rapid scale up of ART in Zambia means that more HIV infected children will be put on treatment. Although ART has significantly reduced morbidity and mortality due to HIV-1 infection [65], liver disease is an increasingly common cause of death among persons infected with HIV in many countries [66]. Recent Studies have shown that there is relatively high liver-related mortality in HIV/HBV co-infection due to the accelerated course of hepatitis B in HIV-seropositive patients. This study will highlight the burden of HBV and HCV infection in HIV infected children in Zambia.

1.3 Research question

Do the HIV infected Children seen at University Teaching Hospital (UTH), Lusaka have high prevalence of HBV and HCV infection?

1.4 Hypothesis

The prevalence of HBV and HCV infection in the HIV infected children seen at UTH, Lusaka, Zambia is less than 15%.

1.5 Objectives

1.5.1 General Objective

To determine the sero-prevalence and risk factors of Hepatitis B and C in HIV infected children seen at UTH in Lusaka, Zambia.

1.5.2 Specific Objectives

1. Determine the prevalence of HBV infection in HIV infected children seen at Paediatric Centre Of Excellence (PCOE) UTH, Lusaka, Zambia
2. Determine the prevalence of Hepatitis C viral infection in HIV infected children seen at PCOE UTH, Lusaka, Zambia
3. Determine the prevalence of Hepatitis B and C viral co-infection in HIV infected children seen at PCOE UTH, Lusaka, Zambia
4. Describe factors associated with prevalence of HBV and HCV in HIV infected Children seen at PCOE UTH, Lusaka, Zambia

CHAPTER TWO

2.0 Literature review

2.1 Hepatitis B

2.1.0 Epidemiology

The prevalence of chronic HBV infection varies greatly in different parts of the world. The prevalence of chronic HBV infection worldwide could be categorized as high (> 8%), intermediate (2- 8%), and low endemicity (<2%) [7].

High Endemicity(> 8%)

Hepatitis B is highly endemic in developing regions with large population such as South East Asia, China, sub-Saharan Africa and the Amazon Basin [8]. In these areas, 70–95% of the population shows past or present serological evidence of HBV infection [8]. Most infections occur during infancy or childhood. Since most infections in children are asymptomatic, there is little evidence of acute disease related to HBV, but the rates of chronic liver disease and liver cancer in adults are high [8].The carrier rate of HBV infection in high endemic area ranges between 10-20 % [7].

Intermediate Endemicity (2-8%)

Hepatitis B is moderately endemic in part of Eastern and Southern Europe, the Middle East, Japan, and part of South America [8]. Acute disease related to HBV is common in these areas because many infections occur in adolescents and adults; however, the high rates of chronic infection are maintained mostly by infections occurring in infants and children[8]. In these areas, mixed patterns of transmission exist, including infant, early childhood and adult transmission [8].The carrier rate of HBV infection in these areas is between 3-5% [7].

Low Endemicity (< 2%)

The endemicity of HBV is low in most developed areas, such as North America, Northern and Western Europe and Australia [7]. The carrier rate of HBV infection in low endemic areas is between 0.1-2 % [7]. In these countries, most HBV infections occur in adolescents and young adults in relatively well-defined high-risk groups, including injection drug users, homosexual

males, healthcare workers, patients who require regular blood transfusion or haemodialysis [8].

The eight known genotypes vary in distribution geographically: predominantly genotypes B and C in Asia; genotype A in Northern Europe; genotype D in the Mediterranean and Middle East; genotype F in South America; and genotypes A and E in Africa [9].

Several studies have been done on the prevalence of Hepatitis B and C viral infection in children in Africa and other parts of the world.

In USA, a chart review of 228 HIV-infected children and adolescents at Jacobi Medical Centre's paediatric HIV clinic showed that 2.6% (6/228) had HBV infection [10].

In Spain, a cross-sectional study of all vertically HIV-infected children and adolescents from 14 hospitals in Spanish cohort of HIV- infected children (a national registry of Spanish HIV-infected patients aged 18 years or younger) during 2011 was conducted. The results showed that 1.2% (3/254) patients were chronically infected with HBV at inclusion (HBsAg+, anti-HBc IgM+, anti-HBs-), 2.4% (6/254) had possible occult HBV infection. No cases of acute HBV infection were detected [11].

In China, a study on HIV-1 infected children under the age of 16 years who were enrolled in China National Paediatric ART Cohort since July 2005 to 2009, showed that a total of 4.9% (53/1082) children tested were HBsAg seropositive [95% confidence interval (CI): 3.6% to 6.2%]. Age was associated with HBV co-infection in univariate analysis; older children were more likely to be HBsAg positive [12]. The possible explanation why older children were more likely to be infected with HBV was that they were less likely to have been vaccinated after birth since they were born before Hep B vaccine was introduced. Besides, it is noted that the prevalence of HBV infection can increase with age due to greater cumulative opportunities for exposure.

A study on the prevalence of HIV/HBV co-infection in Nigerian children found that about 7.7% of HIV infected children had HBV infection [13]. There was no significant association between co-infection with either of the hepatitis viruses and socio-economic status, gender, number of persons living in the household, World Health Organization clinical stage, and route of acquisition of HIV, scarification, blood transfusion, unsafe injection or circumcision.

The lack of association between some of these practices, which have potential for transmission of hepatitis B and C and HIV, may be associated with the current drive for high awareness of HIV, which has increased knowledge of prevention methods, including the observance of universal precautions.

In Ivory Coast, a study on HIV-1 infected children enrolled from October 2000 until December 2003 was carried out. In this paediatric cohort, the prevalence of HBsAg at inclusion was 12.1% [14]. Among the HBV/HIV-1 co-infected children, a high rate of positive HBeAg Chronic Hepatitis B (CHB) was noted at inclusion (82.4% [28 of 34]; 95% CI, 65.5%– 93.2%) and after a median follow-up of 18 months (78.3%; 95% CI, 45.5%– 92.7%) [14]. The study further emphasises the need for routine screening of HBsAg in all HIV positive children at enrolment.

In Kenya a prospective study of 378 consecutive HIV- positive patients aged 13 years and above showed 6.1 % co-infection of HIV and HBV [15]. As may be expected, previous hepatitis B vaccination appeared in this cohort to protect against HBV infection. No patient with previous hepatitis B vaccination developed subsequent hepatitis B infection whereas 7.4% (23/309) who had not been vaccinated were co-infected with HIV and HBV (P=0.001). This study was very important because it showed that Hepatitis B vaccine is very protective even in HIV positive children.

In Tanzania, a study on 167 children infected with HIV aged between 18 months and 17 years old, showed that the overall prevalence of hepatitis viral co-infection among the HIV infected children was about 15% [16]. The prevalence of hepatitis viral co-infection was significantly higher among girls (21.5%) than boys (9.0%)[16]. There was no association between age and hepatitis viral co-infection. The reason for the differences in prevalence in sex was unclear

In Swaziland, a retrospective chart review was done on HIV infected patients enrolled at the clinics from January 2009 to May 2011. Overall, 1.4% (7/500) of the children studied were found HBsAg positive [17].

The studies above all showed that there is still a high burden of viral hepatitis in children. The results also showed that low income countries have high to intermediate endemicity of Hepatitis B. However, the potential for effective international collaboration in this field will

be enhanced when expertise and resources from the developed world are combined with an understanding of the unique priorities and epidemiologic setting of resource-limited countries. Therefore, more studies are needed on epidemiology, natural history, and response to therapy of HBV-HIV co-infection in resource-limited settings mainly from sub-Saharan Africa and the Southeast Asia.

2.1.1 Transmission

HBV is exceedingly resilient and can live for more than 7 days on a dry surface. It is found in semen, vaginal secretions, and saliva, but the highest concentration of virus is in blood [18]. Risk factors for infection in adults include intravenous drug use, cocaine use, promiscuity, and birth in a country with high HBV endemicity. The primary mode of HBV transmission to young children is vertical, although children under 5 years of age are also at risk of horizontal intra-familial transmission. HBsAg can be detected in breast milk, but several studies that have measured the rate of HBV transmission from chronic HBV carriers to breast-fed infants, after proper immunoprophylaxis of the infant, have shown that there is no additional risk of infection from breast feeding [4]. The incubation period for Hepatitis B is 6 weeks to 6 months [19]

2.1.2 Clinical Presentation

The age of an individual when they are initially infected is roughly inversely proportional to the likelihood of them developing a persistent HBV infection. Neonates have a greater than 90% risk of becoming chronically infected with HBV, children and adolescents have a 25–50% risk, and only 5% of adults exposed to HBV develop chronic infection [20]. Patients infected with HBV can present with an acute or chronic infection, although it is far more common for patients to present with chronic infection [21].

2.1.3 Acute infection

The course of acute infection varies from sub clinical to fulminant hepatitis. When classic symptoms occur, they last 2–3 months and include fever, jaundice, abdominal pain, liver tenderness, nausea and vomiting. Acute hepatitis develops at around 2 months of age in 6% of infants born to anti-HBe sero-positive mothers [22]. Classic symptoms are present in 30–50% of older children and adolescents with acute HBV infection, and few children under 5 years of age will have isolated jaundice [23].

2.1.4 Chronic Infection

Chronic infection is defined as persistence of HBsAg for longer than 6 months. Chronic HBV infection is usually asymptomatic and infected children have normal growth, physical examination results, nutritional parameters and development [24]. In perinatally infected children who are less than 4 years of age, estimated spontaneous clearance of HBV (i.e. loss of HBsAg and development of anti-HBs antibodies) occurs at a rate of 0.6% per year over the first decade of life, but the rate of clearance is higher (1.8% per year) in patients infected as adolescents and adults [25]. Of those children who remain infected, most develop immune tolerance and have normal levels of hepatic transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), which in HBV infection is generally reflective of less active hepatic inflammation. Viral replication is also suppressed in most of these patients, with the development of anti- HBe and loss of HBeAg, and either the clearance of or low levels of HBV DNA [26]. Other chronically infected children, however, have ongoing active viral replication as indicated by the presence of HBeAg and elevated HBV DNA levels, frequently with an ongoing inflammatory hepatitis, as indicated by persistently or intermittently elevated transaminase levels (ALT in particular). Most concern has been focused on patients with active hepatitis because 10–20% of these patients will develop cirrhosis over a 20-year period [26]. Patients with cirrhosis are at the highest risk of developing end-stage liver disease and Hepato Cellular Carcinoma (HCC). There is, however, mounting evidence that patients with pre-cirrhotic liver disease who have active viral replication and elevated HBV DNA levels are also at increased risk of developing HCC, based on the oncogenic potential of replicating HBV even in the immunotolerant state [26]. Although it is uncommon, HCC does occur in children with chronic HBV, the youngest reported case was in an 8 month old infant [27]. Paediatric HCC has a poor prognosis, with a long-term survival rate of only 10–30% [28].

2.1.5 Diagnosis

The diagnosis of hepatitis B is made by detecting HBsAg at any time. Acute infection is detected by IgM anticore antibodies to hepatitis B while chronic hepatitis is demonstrated by the presence of IgG anticore antibodies to hepatitis B. Hepatitis Be antigen (HBeAg) may be present in acute or chronic infection, but persistent HBeAg after 6 months suggests a high level of chronic infection. Quantitative assay of hepatitis B DNA indicates the level of viral load and determines infectivity [29].

2.1.6 Treatment

The goal of treatment of viral hepatitis is to decrease viral replication, to lessen symptoms, to improve liver histology with decrease in inflammation and fibrosis, and thus to decrease progression to cirrhosis and HCC and ultimately to improve long-term survival. The table on the next page shows the drugs recommended for the treatment of HBV chronic infection.

Table 1. Drugs recommended for treatment of Chronic HBV infection[26]

Agent	Advantage	Disadvantage	Dose in Children	Dose in Adults
IFN- α	No identified drug resistance Short duration of treatment (16–24 weeks)	Parenteral administration Adverse effects common	For children >2 years of age: 5–10 MU/m ² three times weekly for 24 weeks	5 MU/day for 24 weeks
PEG-IFN- α 2a	Once weekly administration	Parenteral administration Adverse effects common	Not approved	180 μ g/week for 24 weeks
Lamivudine	Minimal adverse effects Oral administration, liquid formulation available	Drug resistance common (~20%/year)	3 mg/kg/day up to 100 mg/day orally for children >2 years of age for \geq 52 weeks	100 mg/day for 52 weeks
Adefovir dipivoxil	Minimal adverse effects Oral administration Effective against lamivudine resistant HBV	Drug resistance (~2% at 2 years)	Not approved	10 mg/day for 48 weeks
Entecavir	Minimal adverse effects, Oral administration High potency in lowering HBV DNA levels in adults	Less effective against lamivudine-resistant mutants	Not approved	0.5 mg/day for 48 weeks
Telbivudine	Minimal adverse effects Oral administration High potency in lowering HBV DNA levels in adults	Drug resistance (~21% at 2 years)	Not approved	600 mg/day for 52 weeks

Abbreviations: IFN- α , interferon α ; PEG-IFN- α 2a, pegylated interferon α 2a.

2.1.7 Prevention

The hepatitis B vaccine is the mainstay of hepatitis B prevention. WHO recommends that all infants receive the hepatitis B vaccine. The vaccine can be given as either three or four separate doses, as part of existing routine immunization schedules. Newborns of HBsAg positive Mother should receive Hepatitis B Immune globulin (0.5mL, IM) and single antigen hepatitis B vaccine (0.5mL, IM) at separate injection sites within 12 hours of birth [19]. The complete vaccine series induces protective antibody levels in more than 95% of infants, children and young adults. Protection lasts at least 20 years and is possibly lifelong [1].

All children and adolescents younger than 18 years old and not previously vaccinated should receive the vaccine. People in high risk groups should also be vaccinated, including:

- People with high-risk sexual behaviour
- Partners and household contacts of infected people
- Injecting drug users
- People who frequently require blood or blood products
- Recipients of solid organ transplantation
- People at occupational risk of hepatitis B virus infection, including health-care workers
- Travellers to countries with high rates of hepatitis B infection

The vaccine has an outstanding record of safety and effectiveness. Since 1982, over one billion doses of hepatitis B vaccine have been used worldwide. In many countries, where 8–15% of children used to become chronically infected with the hepatitis B virus, vaccination has reduced the rate of chronic infection to less than 1% among immunized children [1]

All blood and blood products must be screened for HBsAg, although this screen can miss the small number of occult HBV infections (defined as HBsAg-negative but HBV-DNA positive) [30]. To reduce nosocomial transmission, hospitals must maintain strict observance of universal precautionary measures and specific measures to prevent needle-stick injuries.

2.1.8 Hepatitis B and HIV Co-infection

ART is a double-edged sword in patients with HIV-HBV co-infection: by restoring innate and adaptive immunity, it can induce anti-hepatitis B s and/or anti-hepatitis B e Seroconversion with or without flares of necroinflammatory activity, but it can also cause flares without inducing change of serological status [31]. Three antiretrovirals; lamivudine,

tenofovir, and emtricitabine have “dual” activity and are able to suppress both HIV and HBV replication. Their use as components of ART has been associated with prevention of new infections, histological improvement, and prevention of hepatitis B progression toward cirrhosis and HCC [31]. However, severe reactivations have been seen after withdrawal of medications with anti-HBV activity or after virologic breakthrough related to the occurrence of resistant HBV mutants selected by prolonged exposure to these drugs [31].

It has been demonstrated that lamivudine resistance occurs in more than 90% of HIV-HBV–co-infected patients exposed to lamivudine for more than 4 years [32]. In addition, in HIV-co-infected patients exposed to a failing lamivudine treatment for 3 years, multidrug-resistant HBV strains and potential vaccine-escape mutants have been reported [32].

Tenofovir-disoproxil-fumarate is a potent anti-HBV drug that is effective in suppressing replication of lamivudine-resistant HBV mutants; several studies have clearly established its activity in the face of lamivudine-resistant HBV, with an average reduction of 4 logs in serum HBV DNA [33]. Thus, most of the current guidelines suggest that the combination of tenofovir with either lamivudine or emtricitabine is the preferred choice for HIV-HBV–coinfected patients with the need to treat HIV infection, irrespective of prior exposure to lamivudine; in fact, these 2 combinations have resulted in HBV DNA suppression and normalization of the ALT level, even in patients with lamivudine resistant mutants [34]. Tenofovir use has been associated with rapid and persistent suppression of HBV replication and with reversion of cirrhosis, and it has still not been associated with the occurrence of virological breakthrough because of resistant mutants or to appearance of vaccine escape HBV mutants [34].

2.2 Hepatitis C

2.2.0 Epidemiology

The estimated worldwide prevalence of HCV infection is 3%, which means that nearly 170 million individuals are affected [2]. In the US, the overall sero-prevalence of HCV is 1.8%, which equates to an estimated 2.7 million affected individuals. In children aged 6–11 years, the sero-prevalence of HCV is only 0.2%, and is 0.4% in 12–19 year olds [35]. HCV is classified into six genotypes based on genetic divergence of 30–35% of the nucleotide sites; these genotypes have specific geographical distributions. In the US, genotype 1 accounts for roughly 75–85% of HCV infections, with the remaining 15–25% typically being HCV

genotype 2 or 3 infections [36]. Genotypes 2, 3 and 4 are represented in smaller numbers in the western hemisphere, and genotypes 5 and 6 are limited to Southeast Asia and Africa [36].

In Spain, a study done on HIV infected children showed the prevalence of 0.8% of HCV infection [11]. In the Far East, in China the HCV prevalence was found to be 9.6% in HIV infected children [12].

In West Africa, for example in Nigeria the HCV infection in HIV infected Children was found to be 5.2% [13]. In this study the HCV infection was found to be higher in children aged 5 years and above. In Ivory Coast, a paediatric Cohort study on HIV-1 infected Children found no HCV infection in the studied population [14].

In Kenya, the prevalence was found to be 1.1% in HIV infected patients aged 13 years and above [15]. In Tanzania, a study on HIV infected Children showed a prevalence of HCV to be 13.8% [16]. The prevalence was found to be higher in Children aged less than 2 years and those above 10 years old. In Ethiopia, a cross section study done on HIV positive children at the Felgehiwot referral Hospital showed 5.5% (14/253) [37]. All these studies showed that HCV infection is still a big challenge worldwide, though its prevalence is less than HBV infection.

2.2.1 Transmission

Risk factors associated with HCV infection include parenteral exposure, such as intravenous and intranasal drug use, high-risk sexual behaviour, and transfusion of blood products before 1992. The virus is, however, inefficiently transmitted by sexual activity, so practices that increase the likelihood of blood exposure carry the greatest risk [38]. Although these modes of transmission do apply to the paediatric population, vertical transmission now accounts for the greatest number of new infections [39].

The risk of vertical transmission of HCV is increased by maternal viremia and co-infection with HIV. Rates of transmission in women infected with HCV only range from 3.2–6.4% [40]. By contrast, rates of transmission are 15.1–22.5% for mothers who are co-infected with HIV and HCV [40]. The incubation period for HCV infection is between 14 to 180 days (average of 45 days) [41]

2.2.2 Clinical Presentation

Acute Infection

Few patients (<30%) who have an acute HCV infection experience symptoms of hepatitis (fever, malaise, abdominal discomfort and jaundice) [42]. Most infected individuals are unaware that they are infected until the infection is detected inadvertently or through screening. An acute symptomatic infection in infants is similarly rare, but when it occurs a considerable elevation of ALT levels results and many infants go on to clear the infection [26].

Chronic infection

Most infected individuals (60–80%), regardless of their age at infection, become chronically infected with HCV [42]. Studies of the natural history of HCV in children, however, suggests that young children have a higher rate of spontaneous clearance of virus. In a study of 67 children who were infected via a blood transfusion, 45% had spontaneously cleared the virus 3–20 years after they were infected [43]. Chronically infected individuals are typically asymptomatic, but fatigue, particularly in teens and adults, is commonly associated with persistent HCV infection [44]. Infected patients who present with anorexia, weight loss, abdominal pain, hepatomegaly and splenomegaly are likely to have advanced liver disease [45]. Unlike with HBV, many individuals infected with HCV have normal ALT levels despite necroinflammatory damage in the liver [46].

In prospective studies of adults infected with HCV, 10–15% of those chronically infected developed cirrhosis within two decades [47]. Age at acquisition, duration of infection, and alcohol ingestion can all influence the severity and progression of disease. Overall, the inflammation and fibrosis is less severe in children than non alcohol-drinking adults who have an equal duration of infection, genotype, and concentration of virus in the blood [48].

Although most children who are chronically infected with HCV have mild to moderate inflammation revealed by biopsy of the liver, there is evidence of cirrhosis in up to 5% [48, 49] and some of these will present with end-stage liver disease and require liver transplantation [50].

2.2.3 Diagnosis

Children who fall in one of the high-risk groups described above should be screened for HCV. Screening with anti-HCV antibody is the most cost-effective method of screening, but it must be done after the likelihood of detecting maternal antibody (if the mother is infected) has passed; hence the recommendation to do this testing after a child has reached 18 months of age. If testing is desired before a child is 18 months old, or for verification of active HCV infection in the case of a positive anti-HCV test, detection of HCV RNA is necessary. Regardless of the age of the individual, a positive HCV RNA test documents active viral infection. If HCV RNA is negative, it should be repeated in 6 months, as fluctuating viremia is common in both adults and children [38].

2.2.4 Treatment

Acute HCV

Indications for treatment of acute HCV in HIV infection are the same as those in HIV-uninfected individuals. Treatment is generally not initiated until 12 weeks after initial HCV infection to allow for possible spontaneous clearance, which occurs in 30–50% of mono-infected patients, and in 15–20% of HIV-infected individuals [51]. Sustained Virologic Response (absence of detectable HCV RNA 6 months after cessation of therapy) occurs in 60–80% of subjects with acute HCV [52, 53]. Many experts use combination pegylated interferon and weight-based ribavirin for 48 weeks. In contrast, ribavirin is not used with acute HCV in HIV-uninfected patients and only 24 weeks of pegylated interferon is recommended [51].

Recent studies have suggested that in patients who achieve a rapid virologic response, defined by undetectable HCV viral load by week 4 of treatment, a shortened 24-week course of treatment may be appropriate [52].

In patients who fail to achieve an Early Virologic Response (EVR), defined by < 2 log drop in HCV viral load by week 12 of treatment, or who have detectable HCV RNA at week 24, HCV treatment should be discontinued. Patients with evidence of decompensated liver disease, including ascites, hepatic encephalopathy, and liver-related gastrointestinal bleeding, should generally not initiate HCV therapy due to the risk of further liver decompensation

related to interferon therapy. Liver transplantation for hepatitis C in children is rarely required, but it is a common indication in adults. Re-infection of the graft is almost 100%, despite prophylactic measures such as treatment with antiviral agents and modification of immunosuppression [54].

Chronic HCV

Treatment of chronic HCV in HIV-infected patients is more complex and less algorithmic than treatment of acute HCV. The general approach involves weighing the morbidity associated with pegylated interferon and ribavirin (PEG/R) with the benefits of therapy, while considering the likelihood that an individual patient may actually respond to treatment. Given improved response to HCV therapy in those with well-controlled HIV, treatment of HIV is generally initiated prior to treatment of HCV [51]. However, in cases where ART-related toxicity precludes continuation of ART, HCV may need to be treated first, allowing for improved tolerability of ART. The benefits of HCV treatment in HIV infection include decreased ART-associated hepatotoxicity, regression of liver fibrosis, and decreased risk of decompensated liver disease, decreased liver-related death, and decreased mortality [54]. Predictors of response to HCV therapy in HIV-infected patients include younger age, lower baseline HCV viral load, HCV genotype 2/3 compared to genotype 1/4, and higher CD4 count [55]. Ideally, CD4 count over 350cells/mm³ should be achieved to optimize response to interferon/ribavirin. A recently discovered single nucleotide polymorphism (SNP) near the IL28B gene on chromosome 13 also correlates highly with spontaneous HCV clearance and is one of the strongest predictors of treatment response in HIV-uninfected patients, particularly with HCV genotype 1 [56]. This susceptibility allele is more common in Caucasians and Asians compared to African Americans and may explain much of the racial/ethnic discrepancies in response to HCV therapy. IL28B studies in HIV/HCV.

Co-infected patients also suggest a prognostic utility of IL- 28B in predicting interferon-based response to HCV treatment [56].

Treatment of chronic HCV in HIV-infected patients has traditionally included pegylated interferon and ribavirin for 48 weeks, regardless of HCV genotype. Pegylated interferon (PEG/R) has documented superiority over standard interferon [57]. Guidelines recommend 48 weeks of treatment in HIV treatment experienced HCV patients, regardless of genotype. However, in those who achieve a negative HCV RNA at week 4 of therapy, treatment may be

shortened to 24 weeks [58]. In patients who fail to achieve an EVR, or who have detectable HCV RNA at week 24, HCV treatment should be discontinued. Patients with evidence of decompensated liver disease, including ascites, hepatic encephalopathy, and liver-related gastrointestinal bleeding, should generally not initiate HCV therapy due to the risk of further liver decompensation related to interferon therapy [51].

The introduction of direct-acting antivirals (DAAs) has opened a new era of therapy in HCV, including studies of HCV protease inhibitors and polymerase inhibitors in patients with HCV genotype. PEG/R remains the standard of care for non-genotype 1 HCV patients [51]. Studies in HCV genotype 1 HCV mono-infection have shown that combination DAA and PEG/R have yielded higher Sustained Virologic Response(SVR) rates than PEG/R alone, in both treatment-naive and treatment experienced patients [59]. Two HCV NS3 protease inhibitors, telaprevir and boceprevir, were FDA approved in 2011 for use in combination with PEG/R in genotype 1 HC mono-infected patients [60, 61].

These drugs cannot be used as monotherapy due to rapid emergence of drug resistance. These drugs are currently approved for genotype 1, although studies including genotypes 2/3 are underway. Ribavirin remains essential to prevent relapse [51]. Both protease inhibitors markedly improve the response rates in both naive and treatment-experienced patients with chronic HCV. Boceprevir (Merck, PA, USA) 800 mg must be administered every 8 hours with food in combination with PEG/R. For HCV mono-infected patients, response-guided therapy is recommended: IFN/R is given for a 4-week lead-in, followed by IFN/R and boceprevir. If HCV RNA is undetectable at weeks 8 and 24, therapy is stopped at week 28 in treatment-naive patients and week 36 in treatment experienced patients [62]. If HCV RNA is not undetectable until week 24, then triple therapy is continued for 36 weeks followed by 12 additional weeks of PEG/R [60]. Treatment should be stopped for futility if HCV RNA is equal or greater than 100 IU/mL at week 12 or confirmed detectable at week 24.

CHAPTER THREE

3.0 Methodology

3.1 Study design

This was a Cross-sectional study

3.2 Target Population

HIV positive Children aged 18 months to 15 years old seen at PCOE UTH, Lusaka, Zambia.

3.3 Study Population

HIV positive Children aged 18 months to 15 years old seen at PCOE UTH, Lusaka, Zambia.

3.4 Study site

UTH is the biggest referral hospital in Zambia. PCOE is a state of the art outpatient care, which serves many HIV positive children. It has its own modern laboratory facilities. Consultations are done daily Monday to Friday from 07hrs to 16hrs. The centre was therefore chosen as an appropriate site for the study.

3.5 Eligibility

3.5.0 Inclusion Criteria: HIV positive Children aged 18 months to 15 years old were eligible for the study.

3.5.1 Exclusion Criteria:

- HIV negative Children by antibody test
- Children less than 18 months old and those above 15 years old
- All those that declined to give consent

3.6 Sample Size

The sample size was 187, calculated using Epi-info version 3.5.1 using the expected prevalence of 15% HBV, at 95% confidence interval, from approximately 4000 HIV positive children currently being followed up at ART clinic in PCOE.

3.7 Sampling Method

Systematic sampling of the participants was used. The first and every third patient were invited to participate in the study. Recruitment of the participants was done from Monday to Friday except public holidays and a maximum of 8 Children were recruited in a day.

3.7.0 Study Procedure

All the eligible participants were interviewed. Demographic, medical history, possible risk factors for transmission of viral hepatitis B/C were obtained by an interviewer administered data collection tool (Appendix V). Blood samples (3mls-4mls each) were collected from each participant by venepuncture for haemoglobin, liver enzymes (AST and ALT), and serology tests for HCV and HBV. Hepatitis B and C tests were done from ZNBTS laboratory. Haemoglobin and liver enzymes tests were done at the PCOE laboratory (Chapter 4). Each participant was given a special code for identity. The hospital file number and the study code were recorded in a confidential book that was kept under lock and key for easy correlation with the tests results.

3.8 Ethics

The research was approved by ERES Converge (research ethics committee). Permission was sought from the UTH management through the Head of Department of Paediatrics and child health to carry out the research at the institution.

Written informed consent/assent was obtained from the participants. It was made clear to the participants that their participation in the study was purely voluntary and that they were allowed to withdraw from the study at any time without any prejudice to further medical care if they wished to. Participants were informed that there were no monetary or material benefits in being part of the study. The importance and the benefit of the study, including the possible risks to the participants were explained in the participant information sheet which was translated in Nyanja one of the common spoken local language in Lusaka. The participants were required to sign the consent/assent forms in duplicate, and retained a signed copy. Patient confidentiality was assured as no names were used but individual codes were used on the data collection tool and the information was kept in a locked cabinet, and keys kept by the principal investigator. The participants who were found HBV or HCV positive were referred to the caring physicians for further follow up.

3.9 Data Analysis

Data was entered, stored using Epidata Version 3.1 software and analyzed using SPSS Version 21.0. The Chi-Square (χ^2) and Fisher's exact test were used to determine the association between sex, HBV immunisation status, ART status, sexual activity and Hepatitis infection. The age, CD4 count, liver enzymes were expressed as means and median. The T-test was used to compare means between continuous study variables. The P value of < 0.05 was considered significant. Logistic regression was used to test for confounders.

CHAPTER FOUR

4.0 Laboratory

4.1 introductions

The testing of the samples was done from two separate laboratories. The Hepatitis tests were done from the Zambia National Blood Transfusion service (ZNBTS) laboratory. The liver enzymes and haemoglobin tests were done from the PCOE laboratory.

The ZNBTS laboratory is enrolled on External Quality Assessment (EQA) programme provided by Royal College of pathologists of Australia (RCPA). The site was chosen for testing because of its credibility and good international standing.

4.2 Sample delivery and processing

The blood samples collected were labelled with patient's unique codes, and then taken to PCOE laboratory. The blood sample in the EDTA bottles was centrifuged at 3000 rpm using the bench top centrifuge. About 1-2 mls of the serum were obtained and stored in the cuvetts labelled with patient code. The serum samples were stored at -8°C. The samples were transferred to ZNBTS lab in batches for testing of HBsAg and HCV antibody. The sample processing procedure employed was as outlined in the ZNBTS process description for Transfusion Transmitted Infections (TTI) testing.

4.3 Testing for HBV and HCV

The procedure for testing was as outlined in the Standard Operating Procedures (SoPs) for each assay

4.3.0 Hepatitis B Viral infection test

Technology: Enzyme Immunoassay (EIA)

Platform: AxSYM automated immunoanalysers

Assay: Abbott AxSYM HBsAg Version 2

Backup system for HBsAg;

Assay used: Abbott Murex HBsAg Version 3

Platform: Tecan Reader (washer: Tecan Columbus Plus)

Incubator: Stuart Forced Dry Air Incubator

4.3.1 HCV antibody test

Technology: Enzyme Immunoassay (EIA)

Platform: AxSYM automated immunoanalysers

Assay: Abbott AxSYM HCV Version 3

Backup system for Anti-HCV antibody;

Assay used: Abbott Murex HCV Version 4

Platform: Tecan Reader (washer: Tecan Columbus plus)

Incubator: Stuart Forced Dry Air Incubator

4.4 Scoring of the Global results

The ZNBTS testing algorithm was used on scoring results. The summary of the interpretation of results was as below:

1. An initial negative test results was considered negative
2. An initial positive sample was repeated in duplicate. The sample was taken as positive if at least two out of the three outcomes were positive.

4.5 Results documentation

The results were compiled and signed out by the ZNBTS Medical director. Hard copies of the compiled results were delivered to the principal investigator by ZNBTS.

4.6 Disposal of the Samples

The used test samples were kept in the laboratory for two weeks and thereafter disposed off as per ZNBTS protocol

CHAPTER FIVE

5.0 Results

5.1 General description of the results

From August 2014 to January 2015, a total of 197 participants consented and were enrolled into the study. The participants were all outpatients who were stable coming for routine reviews. All the participants were HIV positive confirmed by rapid test.

Overall, 187 sample results were analysed. Ten samples were not processed for HBV and HCV because the machine read as error.

The sex distribution of the participants was almost equal. There were 98/187 male participants (52.4%) and 89 were females (47.6%), (Table 2). The median age of the participants was 9 years, with inter-quartile range (IQR) of 1.7,15 (Figure 1). Of the parents/guardians to the children studied, 64.2% (120/187) had attained secondary education, 20.3% (38/187) attained primary education, 5.3% (10/187) had no education at all, 9.1% (17/187) had been to college, and 1.1% (2/187) reached university level education. There were 38% (71/187) unemployed parents, 31% (58/187) in formal employment, and another 31% (58/187) in informal employment. A greater proportion of the children seen were from high density residential areas 71.1% (133/187) (Table 2).

There were only 1.1% (2/187) children that had ever received blood transfusion. Only 2.1% (4/187) children had history of scarification, 0.5% (1/187) had history of jaundice, none of the participants had history of sexual intercourse, and none had history of sickle cell disease. There were 32.6% (61/187) children with history of TB. Only 2.7% (5/187) of the participants were not on ART, the rest of the children 97.3% (182/187) were on ART. Among the children that were on ART, 87.9% (160/182) were on 3TC+X+Y combination and 12.1% (22/182) were on Truvada + X combination (Table 2).

Only 29.9% (56/187) of children were on Cotrimoxazole. The percentage of the participants who were taking anti-Tuberculosis drugs was 3.2% (6/187).

Overall, 3.2% (6/187) of the children were born pre-term, the rest were all term babies. The percentage of the children who were delivered at a health institution was 98.4% (184/187), and 1.6% (3/187) were delivered at home.

The proportion of the Mothers who were HIV positive during pregnancy was 29.4% (55/187) and 34.2% (64/187) were negative. Only 36.4% (68/187) had unknown HIV status during pregnancy (Table 2).

PMTCT was only done by 16% (30/187) of the mothers to the participant. Only 67.4% (126/187) of the children had received full HBV vaccine, 1.1% (2/187) had received < 3 doses of HBV vaccine, and 31.6% (59/187) had never received any HBV vaccine (Figure 2). Among the participants analysed, 78.1% (146/187) of the children were in WHO HIV stage 1, 3.7% (7/187) were in WHO HIV stage 2, and 9.1% (17/187) were in WHO HIV stage 3 and 4 (Figure 3). The median ALT was 22, (IQR 6, 117), AST median was 27, (IQR 8, 99), haemoglobin (Hb) median was 12 (IQR 8, 14) and CD count percentage mean was 28.4% (SD= 9.31) (Table 3).

5.2 Hepatitis B and C viral infection prevalence

Overall, 5.9% (11/187) of the children had HBsAg positive, thus the prevalence of HBV infection was 5.9%. Only 0.5% (1/187) of the children tested HCV antibody positive and none had both HBV and HCV co-infection (Table 3).

5.3 Risk factors associated with HBV or HCV infection

Neither child education level nor parent level of education was associated with Hepatitis B status. Also neither the two children that had history of blood transfusion nor the four children with history of tattoos were positive for Hepatitis B. The five children not on ART were not positive for Hepatitis B (Table 4). At 5% significance level, only AST and ALT serum levels were associated with HBV positive, P-values < 0.01 and 0.04, respectively (Table 5).

ART combination (Table 4), AST and ALT levels (Table 5) had P-values < 0.20 in the bivariate analysis. These three variables were fitted into a logistic regression model with the backward selection method applied. The final logistic model did not include ALT (Table 6).

For every elevation of AST level by 1, the odds for positive Hepatitis B status increased by 7% (Odds Ratio = 1.07, 95% Confidence Interval = 1.02 – 1.12, P-value < 0.01). ART combination was not associated with Hepatitis B status, P-value = 0.07 (Table 6). Among the participants who had received HBV vaccine, 4.7% (6/128) were found HBV positive. On the other hand, 8.5% (5/59) of the children who had never received HBV vaccine tested positive for HBV infection. However, there was no significant association between the risk of being HBV positive and the vaccination status (pvalue = 0.32) of the participants (Table 4).

FIGURE 1. Histogram of age distribution of the study participants at PCOE, UTH, Lusaka

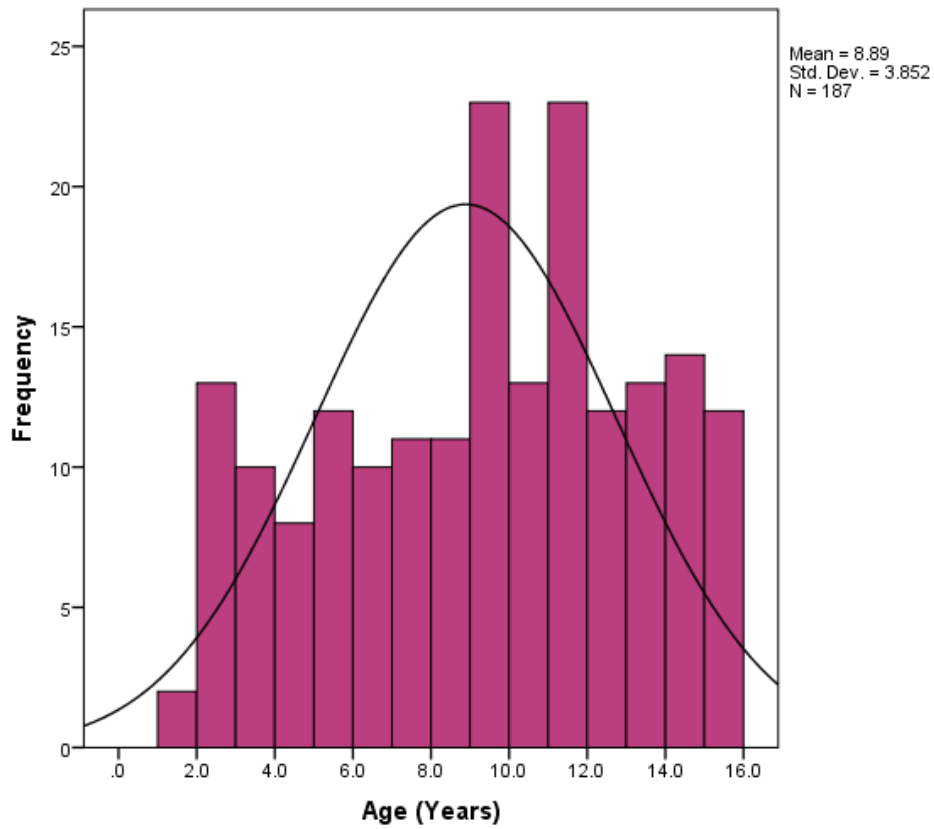


TABLE 2. Summary of the characteristics of the study participants at PCOE, UTH, Lusaka

Age	Median, IQR	9 (1.7, 15)	
		Frequency (n = 187)	Percentage
Sex	Male	98	52.4
	Female	89	47.6
Residence	High density	133	71.1
	Medium density	39	20.9
	Low density	11	5.9
	Rural	4	2.1
History of TB	Yes	61	32.6
	No	126	67.4
ART Combination	Truvada+X	22	11.8
	3TC+X+Y	160	85.6
	Not on ART	5	2.7
Mother HIV Status at delivery	Positive	55	29.4
	Negative	64	34.2
	Unknown	68	36.4
Hepatitis B Vaccine	Fully	126	67.4
	Partial	2	1.1
	None	59	31.6
PMTCT Done or Not Done	Done	30	16
	Not done	157	84
HIV WHO Stage	1	146	78.1
	2	7	3.7
	3	17	9.1
	4	17	9.1

FIGURE 2. Hepatitis B vaccine history of the study participants at PCOE, UTH, Lusaka

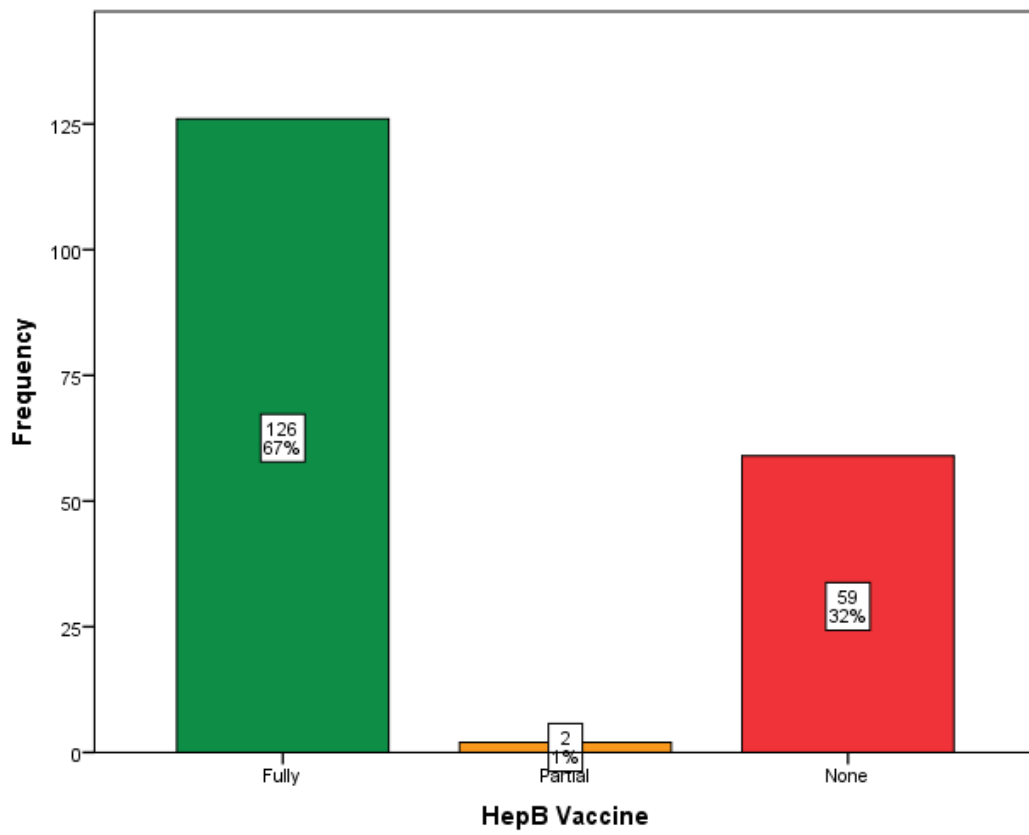


TABLE 3. Summary of the CD4 count, AST/ALT and HBV infection among the study participants at PCOE, UTH, Lusaka

CD4 Percentage		
Mean (SD); Median (Min, Max)	28.4 (9.31); 28 (1, 61)	
Aspartate aminotransferase level		
Mean (SD); Median (Min, Max)	28.8 (9.96); 27 (8, 99)	
Alanine aminotransferase level		
Mean (SD); Median (Min, Max)	23.7 (11.53); 22 (6, 117)	
Hep B Status	Frequency (n)	Percent %
Positive	11	5.9
Negative	176	94.1
Total	187	100
Hep C status		
Positive	1	0.5
Negative	186	99.5
Total	187	100

Note: There was no child who had HBV/HCV co-infection in the study

FIGURE 3. WHO HIV stage characteristics of the study participants at PCOE, UTH, Lusaka

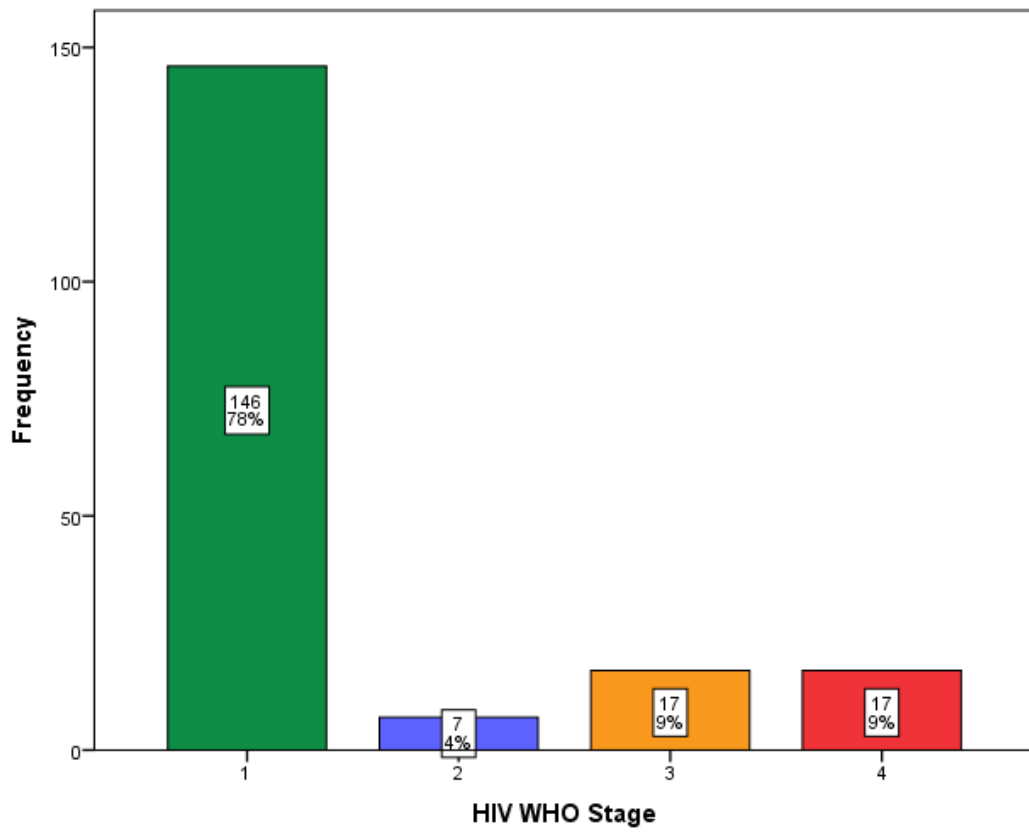


TABLE 4. Bivariate association of the categorical variables with HBV infection among the study participants at PCOE, UTH, Lusaka

Variable	HepB Positive (n = 11)		HepB Negative (n = 176)		Chi-square/Fisher P-value
	N	%	n	%	
Sex					
Male	7	63.6%	91	51.7%	0.44
Female	4	36.4%	85	48.3%	
Child education level					
None	3	27.3%	28	15.9%	0.64
Pre-School	1	9.1%	34	19.3%	
Primary	6	54.5%	87	49.4%	
Secondary	1	9.1%	27	15.3%	
Residence					
High density	10	90.9%	123	69.9%	0.50
Medium density	1	9.1%	38	21.6%	
Low density	0	0.0%	11	6.3%	
Rural	0	0.0%	4	2.3%	
History of TB					
Yes	4	36.4%	57	32.4%	0.75
No	7	63.6%	119	67.6%	
ART Combination					
Truvada+X	3	27.3%	19	11.1%	0.13
3TC+X+Y	8	72.7%	152	88.9%	
Mother HIV status					
Positive	2	18.2%	53	30.1%	0.42
Negative	3	27.3%	61	34.7%	
Unknown	6	54.5%	62	35.2%	
PMTCT					
Done	1	9.1%	29	16.5%	0.99
Not done	10	90.9%	147	83.5%	
Hep B Vaccine					
Full/partial	6	54.5%	122	69.3%	0.32
None	5	45.5%	54	30.7%	
HIV WHO stage					
1	8	72.7%	138	78.4%	0.71
2 and above	3	27.3%	38	21.6%	
Age					
<5 Years	2	18.20%	31	17.60%	0.99
5 Years and above	9	81.80%	145	82.40%	

TABLE 5. Bivariate analysis of the association of the continuous variables with HBV infection among the participants at PCOE, UTH, Lusaka

Variable	HepB Positive (n = 11)	HepB Negative (n = 176)	T-test P-value
Age			
Mean (SD)	9.6 (4.12)	8.9 (3.84)	0.56
CD4 percentage			
Mean (SD)	28.1 (9.70)	28.5 (9.31)	0.90
Aspartate aminotransferase level			
Mean (SD)	38.5 (12.20)	28.1 (9.51)	< 0.01
Alanine aminotransferase level			
Mean (SD)	34.5 (15.41)	23.1 (10.95)	0.04

TABLE 6. Logistic regression analysis predicting positive HBV infection among the children at PCOE, UTH, Lusaka

Variable	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95%CI)	P-value
Aspartate aminotransferase	1.06 (1.02 - 1.11)	1.07 (1.02 - 1.12)	< 0.01
ART Combination			
3TC+X+Y	1	1	
Truvada+X	3.00 (0.73 - 12.29)	3.92 (0.90 - 17.10)	0.07

CHAPTER SIX

6.0 Discussion

The prevalence of HBV infection among the HIV positive children seen at PCOE, UTH in Lusaka is 5.9%. The prevalence of HCV infection was low, at 0.5%. There was no child who had HBV and HCV co-infection among participants. Sexual history, blood transfusion and scarification were not associated with HBV infection. The AST serum level was significantly (95% CI, p value = 0.01) associated with HBV infection.

6.1 HBV and HIV co-infection

Overall the prevalence of HBV among HIV infected children seen at UTH, PCOE was 5.9%. This figure is comparable to prevalence of HBV in sub-Saharan Africa which is between 5-20% [4]. The previous study that was done in Zambia in 1995 on the prevalence of HBV infection among hospitalised children was 6.2% which is comparable to finding in this study. In addition, the ZNBTS data indicates that HBV prevalence among health blood donors is around 10% [5]. This means that Zambia falls in the medium to high endemic area of HBV infection.

The prevalence of HBV infection of 5.9% in this study is comparable to other studies done within the region. In Kenya the prevalence of HBV infection was 6.1% in HIV positive children [15]. However, in this study the prevalence of HBV was less than that found in Tanzania (17%) and in Nigeria (7.7%). The low prevalence found in this study may be due to HBV vaccine protection which was introduced in 2002 (67.4% of the participants had been fully immunised) (Table 2). This was shown by the lower proportion of HBV infection among the immunized participants against HBV 4.7% (6/128) compared to 8.5% (5/59) among the non-immunized. Similarly, Kenyan study found none of the HBV immunised children had HBV infection [15]. In this study, the HBV vaccine status of the participants may not have been a true reflection because none of the participants had brought the children Under-5 card for confirmation of the immunisation record. The information was based on verbal recall. On the other hand, a recent study in Ethiopia found low HBV prevalence of 2.0% among HIV infected children and all study participants were not immunised against HBV [37]. The possible explanation given was that the low prevalence was due to potential effect of anti-HBV of Lamivudine as 87.7% of their study participants were on Lamivudine based ART.

The other possible explanation for the relatively lower HBV infection in our study was due to occult Hepatitis B infection (i.e. absence of serum HBsAg with persistence of low level of intrahepatic HBV DNA), which is very common among the HIV positive individuals [30]. In addition, the prolonged exposure to Lamivudine containing ART could have cleared HBV infection in some individuals. In this study 85.6% of the participants were on Lamivudine based ART combination (Table 1).

6.2 HCV and HIV co-infection

The sero-prevalence of HCV infection was 0.5%. This finding conforms to ZNBTS data that estimates HCV prevalence among adult Blood donors in Zambia to be less than 1% [5]. In Ivory Coast, no HCV infection among HIV infected children was found [16]. In other countries like Spain, the prevalence of HCV among HIV children was found to be 0.8% [11]. These studies agree with our local findings that HCV prevalence is relatively low. In contrast, some studies have shown high prevalence of HCV in some countries. In Ethiopia the prevalence of HCV was found to be 5.5% [37]. In Nigeria, the prevalence was 5.2% in one study done on HIV positive children [13]. In Tanzania, the prevalence of HCV among HIV infected children was 13.8% [16] which was higher than the 1.1% in Kenya and the 0.5% found in this study.

6.3 Risk factors associated with HBV/HCV and HIV infection

In this study local risk factors for hepatitis and HIV co-infection were investigated. The four children who had a history of scarification marks and the two children who had received blood transfusion in the past were not found to have hepatitis infection. Other risk activity like sexual history was not associated with hepatitis infection in this study (Table 2). These results are comparable with study findings in Nigeria where they showed no association between socio-economic status, gender, World Health Organization clinical stage, and route of acquisition of HIV, scarification marks, blood transfusion, unsafe injection or circumcision with hepatitis B/C viral infection [13]. This may be explained due to high awareness of HIV, which has increased knowledge of prevention methods, including the observance of universal precautions. Similarly, none of the local risk factors (blood transfusion, WHO HIV stage, Uvulectomy and Female genital mutilation) factors in Ethiopia were found to be associated with risk of acquiring HBV or HCV infection among HIV infected children [37]. In addition the HIV status of the mother during pregnancy was studied. Majority of the mothers had unknown HIV status at delivery i.e 54.5% (6/11). Only 18.2% (2/11) of the children with

HBV infection had HIV positive mothers during antenatal period. This was not statistically significant (p value = 0.42). The high number of mothers with unknown HIV status during pregnancy could be due to the fact that though HIV testing is part of the antenatal care package offered to pregnant mothers in Zambia, it's an 'opt out' approach, meaning that it's not mandatory and a woman has a choice to decline HIV testing. However the information on whether mother had declined or the service wasn't offered wasn't obtained in this study.

The patient's residential area was one of the risk factors studied in this study. Majority of the participants (90%) with HBV infection were from the high density urban community. None of the children from rural community had HBV infection. This trend was also noted in Ethiopia where the prevalence of HBV/HCV was higher in urban population than rural [37]. However in our study the statistical significance wasn't noted (p value = 0.5)

The immunity of an individual plays a big role in determining the progression to chronic HBV infection. In this study, the immune status of the participants were determined by the CD4 count (absolute and percentage) and the WHO disease clinical staging. Majority of the children with HBV infection were in WHO HIV stage 1, i.e 72.1% (8/11). The mean CD4 percentage was 28.1% (SD=9.70) among the HBV infected children. However the analysis showed no association between the WHO HIV clinical stage and the HBV/HCV infection (p value =0.71). Equally the CD4 percentage wasn't associated with increased risk of HBV/HCV infection (p value = 0.90). In addition, the HBV vaccination status of the participants in this study showed no significant risk to HBV infection (p value = 0.32).

The liver enzymes were also determined. The mean AST among HBV infected children was 38.5 (SD = 12.20) and ALT was 34.5 (SD= 15.41) .After logistic regression AST elevation was found to have significant association with HBV infection (P Value < 0.01). However, the rise in AST serum levels were within the normal reference range and therefore not clinically significant.

This study also showed that the children aged 5 years and above had higher percentage of HBV infection, 81.8% (9/11) as compared to those that were less than five years old, 18.2% (2/11). These findings are comparable to the study results found in Ethiopia where majority of the children who were found to have HBV infection were above the age of five years [37]. This may be attributed to the fact that the older children may not have received the HBV

vaccine since they were born before it was introduced in Zambia. However in this study the age was not statistically significant risk factor for HBV infection (p value = 0.56)

CHAPTER SEVEN

7.0 Conclusion

Overall, HBV infection is common among the HIV positive children seen at PCOE, UTH in Lusaka. The prevalence of HBV among this group is 5.9% which is medium endemic area. The prevalence of HCV infection among HIV positive children seen at the centre is low (0.5%). This study showed that the HBV and HCV co-infection among the studied population is very rare. The low percentage of positive HBsAg test among HBV immunised children (4.7%) compared to the non-immunised (8.5%) showed that HBV vaccine offer protection to HBV infection even in HIV infected children. The only risk factor associated with HBV/HCV infection in this study was AST elevation after logistic regression.

7.1 Limitations

1. HCV viral RNA titre in the patient who had HCV anti-body positive wasn't done. The viral RNA detection would indicate active HCV replication and baseline RNA titre level is a prognostic indicator to treatment. In addition, HCV genotype is another prognostic factor and this test wasn't done as well. Lower HCV RNA titre, genotypes 2 and 3 are associated with good treatment outcome.
2. This study being a cross sectional, HB IgG could not be done at 6 months post HBsAg test to determine if the children have recovered from the infection.
3. The population studied was just based on Lusaka urban and the results may not reflect the national picture on the prevalence of HBV and HCV infection among HIV infected children in Zambia.

7.2 Recommendations

1. All HIV positive children should be screened for HBV infection.
2. HBV testing kits should be made available in all centres involved in the care of HIV positive children.
3. All children found HBsAg positive should have a repeat test after 6 months to determine those with chronic infection (persistence of HBsAg positive longer than 6 months) so that appropriate treatment can be offered.

4. It is further recommended that a large scale study is undertaken in both rural and urban settings to better estimate the prevalence of HBV/HCV infection in HIV positive children in Zambia.

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APPENDIX 1

PEPALA YACHIDZIWITSO YA MAKOLO/WOSUNGA

Mutu waphunziro:phunziro pa kachitidwe ndi zinthu zoopsyeza kalombo kamatenda a Hepatitis B ndi C mu ana ali ndi HIV owonewa pa University Teaching Hospital(UTH)gawo la ana ndi umoyo wa mwana,mu Lusaka,Zambia.Ili ndi phunziro logusana ndi chigawo chaphunziro.

MAU OTSEGULIRA

Dzina langa ndine Chimika Phiri.Ndiphunzira pa University la Zambia pomwe ndichita maphunziro apamwamba a masters Mumatenda mu Ana ndi Umoyo wa Mwana musukulu la Matenda pa UTH.Chonde ndipempha mwana wanu kutengako mbali muphunziro lochulidwa pamwambapa.phunziro iyi ndi gawo lokwaniritsa mwapadera ku mphoto ya Masters mu Ana ndi Umoyo wa Mwana.Mukalibe kuganiza ngati mulola mwana wanu kutengako mbali muphunziro kapena iyayi,ndingakonde kukumasulilani cholinga cha phunziro ndizomwe ziyembekezedwa kwa inu.Ngati muvomera kutengako mbali muzafunsidwa kufwatika pa pepala yachilolezo pamaso pa mboni.Pepala yapadera yachilolezo izapasidwa kwa inu kuti musunge.

Chikhalidwe Ndi Cholinga Chaphunziro

Phunziro iyi iluchitidwa kupeza ndi ana angati ali ndi HIV omwe awonedwa pano pamalo ali ndi matenda a Hepatitis B ndi C.Ichi chichitidwa kuti tiyelekeze bvuto la nthenda iyi mu ana ali ndi HIV owonedwa pa UTH.

Mndondomeko wa phunziro

Ngati muvomera kutengako mbali muphunziro iyi,tizatenga chidziwitso kusewenzetsa pepala yolowetsapo zaphunziro.zokhuzana ndi inu(nambala ya lamy)zizafunika kuti tizikulondolani mwapafupi.4mls ya magazi izatengedwa ku mwana wanu ndikutumidwa ku laboratory kukapimidwa.kukambirana konse kuzatenga mphindi zochepekera makumi awiri.(20 mins)

Zoopsya Zapafupi ndi Zosamvetsa Bwino

mwana wanu sazaopsyezedwa polowa muphunziro.Ngakhale kuti azamva kakuwawa kang'ono kakunyeleti potenga magazi yokapima chomwe chizatengera mphindi zing'ono.

Zothandizira Zapafupi

kulibe thandizo mwa ndalama kapena katundu potengako mbali muphunziro iyi.chidziwitso chomwe tizatenga chizathandiza mwana ali ndi matenda a Hepatitis B ndi C kuti atumiziwe kulanira mankhwala ndipo chidziwitso chotengedwa muphunziro chingathandize opanga malamulo okhuza zaumoyo mudziko kulongosola moyenera ndalama zaumoyo za ana ali ndi HIV mu Zambia.

Chinsinsi

Chidziwitso chizasungidwa mwachinsinsi ndipo dzina la mwana wanu silizasewenzetsedwa, koma nambala yapadera izaikidwa pa pepala.pepala yachidziwitso izasungidwa mumalo okhomera ndipo fungulo(makiyi)yazasungidwa ndi ofufuza.kulibe chizindikiritso chizasewenzetsedwa mukuulutsa zotuluka muphunziro.

Chilolezo Chaufulu

kutengako mbali kwa mwana wanu ndimwaufulu ndipo sazavutisiwa mnjira iliyonse ngati mwaganiza kusatengako mbali muphunziro iyi.Mungachoke muphunziro nthawi iliyonse pachifukwa china chilichonse popanda kukhuza mwana wanu.

Munthu Owona

Zikomo poganiza kutengako mbali muphunziro iyi.Ngati muli ndi mafunso,nkhawa ,ndizofunika kumasulira,chonde onani Dr Chimika Phiri kapena ERES CONVERGE IRB pa keyala iyi

Dr Chimika Phiri

The University Teaching Hospital

Department of Paediatrics and Child Health

P/Bag RW1X,

Lusaka,Zambia.

Nambala ya lamy: 260-974-274080

ERES CONVERGE IRB

33 Joseph Mwilwa Road

Rhodespark

LUSAKA

Lamy: 0955 155633/4

APPENDIX II

PEPALA YACHIOLEZO

Ndimvetsa zonse zili pamwamba zamasululidwa ndipo ndizomveka bwino zamuphunziro iyi ndipo kulibe chikakamizo.Ndilola mwaufulu kutengako mbali muphunziro.

Dzina.....
.....

Chibale.....Kholo/wosunga(chongani)

kusayina.....kapena kufwatika chala chakudzanja

lamanja..... Tsiku.....

Dzina la mboni.....kusayina.....kapena kufwatika

chala chakudzanja lamanja.....Tsiku.....

APPENDIX III

Pepala yachidziwitso ya Otengako mbali (mwana)

Mutu Wa Phunziro :phunziro pakachitidwe ndi zinthu zoopsyeza kalombo ka matenda a Hepatitis B ndi C mu ana ali ndi HIV owonewa pa University Teaching Hospital (UTH) gawo la ana ndi umoyo wa mwana,mu Lusaka,Zambia.ili ndi phunziro logusana ndi chigawo chaphunziro.

wofufuza wamkulu: Dr Chimika Phiri

Kodi kafukufuku ka phunziro ndichiani?

.kafukufuku ka phunziro ndi njira yopezelamo chidziwitso chatsopano chachinthu.Ana safunika kukhala mukafukufuku kaphunziro ngati safuna.

Chifukwa ndichiani mufunsidwa kutengako mbali mukafukufuku kaphunziro iyi?

mufunsidwa kutengako mbali mukafukufuku kaphunziro iyi chifukwa tiyesetsa kuphunzira zambiri zakuvuta kwa Hepatitis B ndi C mu ana ali ndi matenda a HIV mu Zambia.Tikufunsa kukhala muphunziro chifukwa kutengako mbali kwako kuzathandizira pachidziwitso chofunika kwambiri kuthandiza kuona chomwe yachita matenda aya.

Ngati walowa muphunziro ndichiani chizachitika kwa iwe?

.Tifuna kukuuza mwa zinthu zizachitika kwa iwe ngati uli muphunziro iyi.

.Tizakufunsa mafunso ochepa,zirichabe bwino ngati siuziwa yankho.

.Tizasewenzetsa nyeleti kutenga magazi(2mls by 3bottles) ku dzanja lako.

.kukambirana ndikutenga magazi kuzatenga pafupifupi mphindi makhumi awiri(20 mins)

Kodi mbali iliyonse yaphunziro izawawa?

.Inde kutenga magazi yokapimiwa sikuzamveka bwino ndipo kuzawawa.

Kodi phunziro izakuthandiza?

.Inde ngati wapezeka ndi matenda a Hepatitis B/C uzatumidwa kulandira thandizo.Ngakhale kuti kupima magazi kwapeza kuti ulibe,phunziro izakuthandiza kudziwa kuti ulibe matenda.

Kodi Phunziro izathandiza ena?

.inde chifukwa chidziwitso chotengedwa muphunziro iyi chizathandiza akulu a boma ndi ena othandizira ,kupanga chionjezero choyenera kusamalira ana odwala HIV mu Zambia.

.phunziro iyi inamasululidwa bwino ku makolo ako ndipo akamba kuti tingakufunse ngati ufuna kukhalamo.Ndiwe omasuka kukambirana nawo ukalibe kuganiza kutengako mbali.

Ndani azaona chidziwitso chotengedwa cha iwe?

.Chidziwitso chotengedwa cha iwe muphunziro iyi chizasungidwa mosamalira mokhomera.kulibe azaziwa pokhapo anthu ochita kafukufuku.

.phunziro yachidziwitso chaiwe izapatsidwa kumakolo ako ndi adotolo.akafukufuku sazauza anzako kapena wina aliyense.

Utengapo chiani pokhala muphunziro?

.Kulibe ndalama kapena katundu izapatsidwa kwa iwe koma uzakhala ndi mpata wodziwa ngati uli ndi Hepatitis B/C kapena ulibe.

Ufunika kukhala muphunziro?

.siufunika kukhala muphunziro.Palibe azakalipa ngati sufuna kuchita muphunziro iyi.Ngati sufuna kukhala muphunziro iyi,ufunika chabe kutiuza,chili kwa iwe.

.Ungatenge mwa nthawi kuganiza zakukhala muphunziro.

Ngati uli ndi mafunso yaliyonse?

.Ungafunse funso iliyonse yomwe ungakhale nayo yaphunziro.Ngati uli ndi funso pambuyo pake yomwe siunaganize lomba ungatume kapena uza makolo/wokusunga atumile Dr Chimika Phiri pa nambala iyi; 260974274080.

.Ungatengenso nthawi kuganiza pakukhala muphunziro ndikukambirananso ndi makolo pazakukhala muphunziro.

Ulindizitsankho zotani ngati wakamba iyayi kuphunziro iyi?

.Ndiwe omasuka kwambiri kuonedwa pa University Teaching Hospital pamatenda ako.

Zidziwitso zina za phunziro.

.Ngati waganiza kukhala muphunziro chonde lemba dzina lako pansi apa.

.Ungasinthe maganizo ndikuleka panthawi iliyonse.chomwe ufunika kuchita ndikundiiza ine(Dr Chimika Phiri).Akafukufuku ndi makolo ako sazakalipa.

APPENDIX IV

PEPALA YACHIOLEZO

Kodi Uzatengako mbali muphunziro iyi?

.Inde ndizakhala mukafukufuku kaphunziro iyi

.Iyayi sindifuna kuchita ichi.

.....
.....

Kusayina kwa mwana/kufwatika chala chachikulu.

.....
.....

kusayina kwa womusunga/kufwatika chala chachikulu.

.....
.....

kusayina kwa munthu wotenga chilolezo.

Tsiku:.....

