Patterns of liver injury in HIV-positive patients in the medical admissions ward at Chris Hani Baragwanath Academic Hospital (CHBAH)

Dr. Rudzani Wendy Ndwambi
Student Number: 2302007
Supervisors: Prof Reidwaan Ally and Dr. Nazeer Chopdat
Dissertation for Master of Medicine in Internal Medicine

The study is submitted in partial fulfilment for the Degree of Masters of Medicine in Internal Medicine.

Declaration

I, Dr. Rudzani Wendy Ndwambi, declare that this dissertation is my work and is being submitted in partial fulfilment for the degree of Master of Medicine in Internal Medicine at the University of Witwatersrand, Johannesburg.
This work has yet to be submitted for any degree or examination at this institution or other universities.

Signed: RW Ndwambi
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Date: 19/04/2024
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Acknowledgement

I thank my supervisors, Prof Reidwaan Ally and Dr. Nazeer Chopdat, for their motivation, guidance, and inspiration on this research project. I thank the Department of Internal Medicine head for permitting the research in admissions ward 20. Mr. Thabo for assistance in retrieving the patients' files for the study.

Special thanks to my loving, supportive husband, Dr. Michael N. Ndwambi, my children (Bella and Max), family, and friends for continuous support and encouragement.

I am grateful to the Almighty God for his strength and wisdom.

Abstract

Background

Human immunodeficiency virus (HIV) infection is a major global public health concern, with approximately 37.9 million people living with HIV and acquired immunodeficiency syndrome (AIDS) as of 2018. There has been an increase in HIV prevalence globally, with the African sub-Saharan region carrying a disproportionate burden, accounting for more than 70% of this burden. In 2018 South Africa had 7.52 million people living with HIV/AIDS (PLWHA), with approximately 115167 AIDS-related illnesses. In PLWHA, liver disease and failure contribute to more significant morbidity, mortality and higher cost of care.

Aim And objectives

To recognise and categorise the patterns of liver injury in people living with HIV and AIDS (PLWHA).

To ascribe an etiology to the pattern of liver injury in PLWHA.

Method

This was a retrospective cohort, conducted at CHBAH medical admissions ward in Soweto Gauteng province, of patients living with HIV and AIDS with liver injury.

All patients admitted to the medical admissions ward were selected and their hospital numbers retrieved from the admission register. Each hospital number was entered into the NHLS labtrack system to retrieve the LFT results. Any patient with abnormal LFT was checked for their HIV status. The two variables (abnormal LFT and HIV test) were matched and confirmed. After ethics approval was obtained, files were recorded and analysed. A data collection sheet was populated with all serological, histological and radiological investigations documented.

Results

This study included 208 patients (PLWHA) admitted to the medical admissions ward at CHBAH, with abnormal liver enzymes between January 2019 and March 2020, aged above 18 years. One hundred and five, 50.5% were males with a mean of 43.7 years, and 49.5% (n=103) were females with a mean of 39.9 years. One hundred and forty-three, 81.3% were taking antiretroviral therapy (ART), with the majority, 88.4% (n=107), on the first-line regimen. The most common pattern of liver injury was infiltrative, accounting for 67.8% (n=141), followed by mixed at 22.1% (n=46), hepatocellular at 7.7% (n=16), and lastly was cholestatic with 2.4% (n=5). Irrespective of the pattern of the liver injury, 36.1%

(n=75) of the patients had Mycobacterium tuberculosis (MTB) infection, and 22.5% (n=40) of them were on antituberculosis treatment (ATT), 6.3% (n=13) had hepatitis B viral (HBV) infection, 0.5% (n=1) had hepatitis C (HCV) infection, while lymphomas (Hodgkin and non-Hodgkin lymphomas) contributed 1,9%(n=4) and 6,3% (n=13) respectively. Twelve, 5.7% (n=12) had drug induced liver Injury (DILI), and retroviral disease (RVD) cholangiopathy contributed 1.4% (n=3). A significant number of patients, 34.1% (n=71), contributed to at least one-third of patients in the study, wherein the diagnosis was either unknown or not directly related to the liver injury. Those were, Other opportunistic infections accounting for 7.7% (n=16), other diagnoses made up 13% (n=27), and no diagnosis at 13.4% (n=28).

Of the infiltrative pattern, 33.13% (n=47) had MTB infection, 5.6% (n=8) had HBV, 0.3% (n=1) had HCV infection, 7.8% (n=11) had non-Hodgkin lymphoma, with Hodgkin lymphoma, and DILI both accounting for 1,4%(n=2). Only 5.7% (n=12) of PLWHA had liver biopsies done.

Conclusion

Liver injury is common in PLWHA. The most common pattern of liver injury is an infiltrative pattern, and the most common etiology was MTB infection in this study.

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Chapter 1

The research protocol and extended literature review

TITLE

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Dr Rudzani Wendy Ndwambi

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MMed: Internal Medicine

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1. Introduction

Human Immunodeficiency Virus (HIV) infection is a major global public health concern, with approximately 37,9 million people living with HIV as of 2018 (1). There has been an increase in HIV prevalence globally, with the African sub-Saharan region carrying a dis-proportionate burden, accounting for more than 70% of this burden. In 2018 South Africa had 7,52 million people living with HIV/AIDS (PLWHA), with approximately 115167 AIDS-related illnesses (2). In PLWHA, liver disease and failure contribute to more significant morbidity, mortality, and higher cost of care (3).

2. Epidemiology

A South African study by Hoffman (4) showed that 4% of PLWHA had abnormal LFT, which was five times the upper limit of normal before antiretroviral therapy (ART). Kasper and his

colleagues found that 13-18% of PLWHA died from liver-related causes (5). A Nigerian study found that 87% of their cohort had abnormal LFTs; of the hundred and twenty-nine (129) cases they reviewed, 14% showed a cholestatic pattern of liver injury, 83% were hepatocellular, and 3% mixed (6).

3. Definitions

LFTs reflect the concentrations of various proteins and enzymes in the blood that are either produced by the liver cells or released when liver cells are damaged. They measure synthetic, biliary, and intracellular functions. Abnormalities of these proteins/enzymes reflect abnormalities of these descriptive patterns.

Abnormal LFTs are characterized by elevations of alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and bilirubin (BIL) levels. In addition, a reduction in total protein/albumin may reflect diminished synthetic capacity.

Though varied amongst laboratories, the upper limit of normal (ULN) is generally within similar ranges (7). ULN; ALT=40units per litre (u/l); AST =40u/l; ALP =130u/l; GGT =60u/l and total bilirubin (TBIL) =20 micromoles per liter (mmol/l). Any one value exceeding the ULN is considered abnormal (8).

Liver disease can be described according to the abnormal LFT patterns, the molecular mechanism of the liver injury, or the etiology of liver injury (9).

4. Patterns of liver injury

Liver enzyme abnormalities are common in PLWHA, and these abnormalities are classified as either hepatocellular, cholestatic, or mixed/infiltrative (10). It is essential to recognize and differentiate these patterns of liver injury because they can have different etiological and pathophysiological mechanisms. This arbitrary classification is not restrictive, since several diseases and drugs can present with more than one pattern of liver injury. However, early recognition may help identify the most suggestive cause and prevent unnecessary investigations and delay in starting appropriate therapy in PLWHA (5).

4.1. Hepatocellular injury

Acute cellular rupture releases more ALT (intra-cytoplasmic enzyme), whereas persistent and chronic disease will eventually elevate AST (intra-mitochondrial enzyme). When the

primary injury is to the hepatocytes, ALT and AST levels are elevated, with AST being less specific (found in other tissues as well) than ALT (liver-specific). In viral, ischaemic, and drug-induced hepatitis, ALT is elevated more than AST or ALP (7) since it reflects acute rupture of the cell. Slower onset and chronic diseases are associated with longstanding cell destruction and hence greater AST levels, an example being chronic alcohol abuse.

4.2. Cholestatic injury

The ALP and GGT levels are elevated in cholestatic disease since the primary injury is to the bile ducts/collecting system. Bile duct inflammation and obstruction lead to cholestatic injury (7). According to the literature, cholestasis may be extrahepatic (choledocholithiasis, malignant obstruction) or intrahepatic (drug toxicity, infiltrative diseases, viral hepatitis). Nevertheless, some diseases, e.g., AIDS cholangiopathy, may affect the intrahepatic and extrahepatic biliary systems.

4.3. Infiltrative patterns

An infiltrative pattern occurs when the disease affects both the hepatocytes and the bile ducts. It is often seen when the liver is infiltrated or replaced by a granulomatous or malignant infiltration (7). True extrahepatic obstructive causes also elevate the bilirubin (conjugated), whereas these mixed patterns have significant elevations of the ALP/GGT without elevating the bilirubin.

Often, the only way to differentiate infiltrative patterns from obstructive patterns is through liver imaging (ultrasound, computerized tomography scan, magnetic resonance imaging, or cholangiography) and biopsy.

4.4. Mixed patterns

In a mixed pattern, there is both cholestatic and hepatocellular enzyme elevation, as well as elevation in bilirubin.

5. Guidelines to ascribe liver injury and severity

The European association for the study of liver (EASL) uses a grading system for the severity of the liver injury. This system was recently modified while evaluating their cancer therapy program (11) and is accepted as robust and applicable. In this system, the following ranges are used to assess the liver injury and severity:

FEATURE	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ALT (u/l)	<3 x ULN	3-5 x ULN	5-20 x ULN	>20 x ULN
AST (u/l)	<3 x ULN	3-5 x ULN	5-20 x ULN	>20 x ULN
ALP (u/l)	<2.5 x ULN	2.5-5 x ULN	5-20 x ULN	>20 x ULN
Bilirubin (mmol/l)	<1.5 x ULN	1.5-3 x ULN	3-10 x ULN	>10 xULN

Grade 1 indicates mild liver injury, grade 2 moderate liver injury, grade 3 severe liver injury, and grade 4 life-threatening liver injury (8).

6. Mechanisms of liver injury

The molecular events that disrupt cellular transport function are complex and interactive. They can either be biochemically or immune-mediated. The biochemical-mediated liver injuries are mainly via the cytochrome p-450 and conjugation reaction systems. The toxic metabolites may alter the plasma membrane and mitochondrial function, change intracellular ion homeostasis, or interfere with enzyme activity. The immune-mediated liver injuries are through immunological interference by various cytokines, nitric oxide, and complement systems (5).

Overlapping factors contribute to the development of liver injury and hepatic fibrosis. In HIV-infected individuals, albeit the molecular events mentioned above are the same as in non-HIV-infected individuals, there is the added burden of HIV itself and ART therapy (20).

A single disease state often employs several mechanisms in its pathogenesis (5). Therefore, a broad understanding of these mechanisms and linking them to diseases that employ them may be helpful to both clinicians and investigators caring for PLWHA and liver disease.

7. Etiologies

According to Sterling (10), the alterations and abnormal LFTs that occur in PLWHA are often caused by different etiologies coexisting together.

7.1. Infective causes

Several infective agents (viral, bacterial, fungal, or parasitic) cause liver injury that can be hepatic, cholestatic, or mixed. Viral infections, e.g., viral hepatitis B, C, E, cytomegalovirus (CMV), and Epstein-Barr virus, cause hepatocellular injury with AST and ALT levels >25 times the ULN being the predominant pattern. Bacterial infections (e.g., syphilis), disseminated fungal infections (histoplasmosis and cryptococcosis), and parasitic infections (toxoplasmosis, isosporidiosis, and cryptosporidiosis) can cause either hepatocellular or mixed/ infiltrative patterns (13).

7.2. Granulomatous diseases

Granulomatous diseases (sarcoid, amyloid, and tuberculosis) have also been associated with liver involvement in either HIV-infected or non-HIV-infected individuals. They usually present with a mixed pattern that may appear similar to cholestatic injury.

7.2. Drugs and toxins

Alcohol, antituberculosis therapy (ATT), and antiretroviral therapy (ART) are associated with the highest risk of drug-induced liver injury (DILI)(12). Drugs and toxins can cause hepatocellular, cholestatic, or mixed patterns.

Studies have found that drug-associated hepatotoxicity and viral hepatitides are the most common causes of liver disease in PLWHA (13).

7.5. Malignancies

Kaposi's sarcoma and lymphoma are commonly associated with HIV and have been shown or associated with liver injury in PLWHA (13). The other malignancy implicated in liver injury in PLWHA is hepatocellular carcinoma (HCC). It has recently been found that hepatitis, immunosuppression due to HIV, the direct impact of HIV on liver parenchyma, and the use of hepatotoxic ARVs, all can contribute to HCC pathogenesis (14).

7.6. Autoimmune

Autoimmune liver injury, though rare, can occur in patients with well-controlled HIV infection (15).

7.7. Vascular

HIV-infected patients can present with a vascular occlusive disease that can impair blood flow to other organs, including the liver (ischaemic liver injury) (16).

It is anticipated that the findings of this study will help guide the management plans for PLWHA presenting with liver injury at Chris Hani Baragwanath Academic Hospital (CHBAH).
Recognition of liver injury patterns will help clinicians develop a more focused approach to ascribing etiology and instituting appropriate management plans more readily.

8. Aims

8.1. To recognize the patterns of liver injury in PLWHA presenting to the medical admissions ward at CHBAH
8.2. To ascribe an etiology to the pattern

9. Study objectives

9.1. To be able to recommend a more straightforward management plan in diagnosing and treating PLWHA who have abnormal LFTs

10. Outcomes

10.1. To provide an understanding of patterns of liver disease in PLWHA
10.2. To provide a straightforward approach to the management of liver injury in PLWHA

11. Methods

11.1. *Study design*: A retrospective, cohort study.
11.2. *Site of study*: Chris Hani Baragwanath Academic Hospital medical admissions ward.
11.3. *Study population*: Patients over the age of 18 years who are living with HIV and have abnormal liver enzymes.
11.4. *Sampling*
11.4.1. *Sample size*: All HIV-positive patients admitted to the medical admissions ward with abnormal LFTs from January 2019 to March 2020. Test files were reviewed for further analysis using a frequency rate of approximately 14% (average from previous studies) of the HIV-positive patients with abnormal liver function.
11.4.2. *Selection of subjects*: Subjects for the study were selected from the CHBAH Ward 20 admission register. Patients with HIV and abnormal LFT were selected, and their hospital numbers were retrieved from the admission register. Each hospital number that was retrieved was entered into the NHLS lab track system to retrieve the LFT results, and any patient with abnormal LFTs was checked if they had an HIV test done. The two variables (abnormal LFT and HIV test) were matched and confirmed, and the patients' names and

hospital numbers with the confirmed abnormal LFTs and HIV tests were recorded. After ethics approval was obtained, patients files were retrieved from the CHBAH filing room. Data from these patients' files were recorded and analyzed. A data collection sheet (see appendix) was populated with all serological, histological, and radiological investigations available and documented.

11.4.3. *Inclusion criteria*: All patients over the age of 18 who are HIV positive and were admitted via the medical admissions ward with abnormal LFTs.

11.4.4. *Exclusion criteria*: Those with normal LFTs and negative HIV tests

12. Data collection

Once patients have been identified from the ward 20 admission registry, their HIV test and LFTs correlated, their hospital files were retrieved, and all necessary information extracted. This information was entered into a data collection sheet (see appendix) without identifying the patients. All screened cases were reviewed for clinical presentation, clinical examination findings, investigations done, and provisional diagnosis ascertained by the attending physicians. Further information, including CD4 cell counts, viral loads, and other investigations, was accessed via the NHLS laboratory results portal and analyzed. The data collection sheets and records were electronically recorded through Redcap. Patterns of liver injury were recorded as described earlier. All other information that led to the diagnosis was also recorded.

For this study, all other relevant available investigations, e.g., bilirubin and ammonia levels, international normalized ratio (INR), prothrombin time (PT), albumin, glucose, viral hepatitis serology, cytomegalovirus (CMV) staining, alpha-fetoprotein (AFP), Imaging and endoscopy and histology were also used for analysis.

13. Data analysis

After the data had been collected, a statistician was consulted. Statistical analysis was undertaken to compute measures of central tendency (mean, median, and mode) and dispersion measurements (standard deviation, range, variance) where appropriate. The distribution of continuous variables, such as age, was expressed as medians. Frequency tables were generated for gender, ART regimen, CD4 cell count, and viral loads. Testing for the significance of association for categorical data was performed using the Pearson chi-square test. For non-normal distributed data, non-parametric tests, I.e., Mann-Whitney test, to test associations were used. The analysis was performed using STATA version 14

statistical software. Results were displayed in tables. All tests were performed at a 95% confidence interval for statistical significance p-value <0.05.

The data sheet is attached.

14. **Ethics**

Ethical approval for the study submitted to the Wits human research ethics committee was obtained (attached). Permission from the Head of Internal Medicine to conduct the study was requested and granted(attached).

15. Timing

The expected duration of the study:

	September 2019	**October 2019**	**January 2020**	**June 2020**	**July 2020**	**December 2020**
Literature review						
Protocol preparation						
Protocol assessment						
Ethics approval						
Data collection						
Data analysis						
Writing up thesis						

16. Funding

The expenses of this study, including the printing of documents, were personally funded.

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Chapter 2 (Submissible format)

Patterns of liver injury in HIV-positive patients in the medical admissions ward at Chris Hani Baragwanath Academic Hospital

Authors: Dr. RW Ndwambi, Prof R Ally, Dr. N Chopdat

Abstract

Background

Human immunodeficiency virus (HIV) infection is a major global public health concern, with approximately 37.9 million people living with HIV and acquired immunodeficiency syndrome (AIDS) as of 2018. There has been an increase in HIV prevalence globally, with the African sub-Saharan region carrying a disproportionate burden, accounting for more than 70% of this burden. In 2018 South Africa had 7.52 million people living with HIV/AIDS (PLWHA), with approximately 115167 AIDS-related illnesses. In PLWHA, liver disease and failure contribute to more significant morbidity, mortality and higher cost of care.

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To ascribe an etiology to the pattern of liver injury in PLWHA.

Method

This was a retrospective cohort, conducted at CHBAH medical admissions ward in Soweto Gauteng province, of patients living with HIV and AIDS with liver injury.

All patients admitted to the medical admissions ward were selected and their hospital numbers retrieved from the admission register. Each hospital number was entered into the NHLS labtrack system to retrieve the LFT results. Any patient with abnormal LFT was checked for their HIV status. The two variables (abnormal LFT and HIV test) were matched and confirmed. After ethics approval was obtained, files were recorded and an-

alysed. A data collection sheet was populated with all serological, histological and radiological investigations documented.

Results

This study included 208 patients (PLWHA) admitted to the medical admissions ward at CHBAH, with abnormal liver enzymes between January 2019 and March 2020, aged above 18 years. One hundred and five, 50.5% were males with a mean of 43.7 years, and 49.5% (n=103) were females with a mean of 39.9 years. One hundred and forty-three, 81.3% were taking antiretroviral therapy (ART), with the majority, 88.4% (n=107), on the first-line regimen. The most common pattern of liver injury was infiltrative, accounting for 67.8% (n=141), followed by mixed at 22.1% (n=46), hepatocellular, at 7.7% (n=16), and lastly was cholestatic with 2.4% (n=5). Irrespective of the pattern of the liver injury, 36.1% (n=75) of the patients had Mycobacterium tuberculosis (MTB) infection, and 22.5% (n=40) of them were on antituberculosis treatment (ATT), 6.3% (n=13) had hepatitis B viral (HBV) infection, 0.5%(n=1) had hepatitis C (HCV) infection, while lymphomas (Hodgkin and non-Hodgkin lymphomas) contributed 1,9%(n=4) and 6,3% (n=13) respectively. Twelve, 5.7% (n=12) had drug induced liver Injury (DILI), and retroviral disease (RVD) cholangiopathy contributed 1.4% (n=3). A significant number of patients, 34.1% (n=71), contributed to at least one-third of patients in the study, wherein the diagnosis was either unknown or not directly related to the liver injury. Those were, Other opportunistic infections accounting for 7.7% (n=16), other diagnoses made up 13% (n=27), and no diagnosis at 13.4% (n=28).

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Conclusion

Liver injury is common in PLWHA. In this study, the commonest pattern of liver injury was infiltrative and the most frequent aetiology of MTB infection.

Background

Human immunodeficiency Virus (HIV) infection is a major global public health concern, with approximately 37,9 million people living with HIV as of 2018 (1). There has been an

increase in HIV prevalence globally, with the African sub-Saharan region carrying a disproportionate burden, accounting for more than 70% of this burden. In 2018 South Africa had 7,52 million people living with HIV/AIDS (PLWHA), with approximately 115167 AIDS-related illnesses (2). In PLWHA, liver disease and failure contribute to more significant morbidity, mortality, and higher cost of care (3).

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Methods

A retrospective cohort study at CHBAH medical admissions ward in Soweto, Gauteng Province, South Africa. The study included patients who are over the age of 18 years living with HIV and have abnormal liver enzymes from January 2019 to March 2020. Medical records of patients admitted to the medical admissions ward were reviewed for further analysis using frequency rate of approximately 14% (average from previous studies) of HIV-positive patients with abnormal liver function. Subjects for the study were selected from the CHBAH ward 20 admission register. Patients hospital numbers from admission register were retrieved. Each hospital number that was retrieved was entered into the National health laboratory services (NHLS) labtrack system to retrieve liver function test (LFT) results. Any patient with abnormal LFT was checked for their HIV status if HIV test was done. The two variables (abnormal LFT ands HIV test) were matched and confirmed. Patients' names and hospital numbers with confirmed abnormal LFT and HIV tests were recorded. After ethics approval was obtained, patients files were retrieved from the

CHBAH filling room. Data from these patients files were recorded and analysed. A data collection sheet (see appendix) was populated with all serological, histological and radiological investigations and documented. All HIV positive patients with deranged liver enzymes irrespective of any preexisting conditions were included in the study, excluding those with normal LFT and negative HIV test.

Medical records of patients admitted to the medical admissions ward were sought from the CHBAH filing room for the period between January 2019 to March 2020. Ethical approval was obtained to conduct this study from the Witwatersrand health research ethics committee (HREC), ethic number M200315. Permission to conduct the study at CHBAH was also granted by the Chief executive officer, a medical advisory committee (MAC), and the head of the internal medicine department.

The medical admissions ward at CHBAH is one of the busiest wards in the hospital, with approximately 90 patients being admitted via the ward daily and approximately 15-20% of these patients being retroviral disease positive. The study included 208 PLWHA over the age of 18 years. The age group of the study was between the ages of 18 and 76 years, with a mean average of 41.8 years. For this study, files were collected and reviewed for the age, gender, ART and regimen, CD4 and viral load, preexisting liver disease, comorbid disease and treatment, toxins including alcohol and herbal medications, as well as clinical presentation, clinical examination, hepatic biochemistry, serological markers, Imaging and tissue biopsy including liver biopsy.

A statistician was consulted for data analysis. Quantitive methods were used to analyze the data. Stata 16.1 (StataCorp, College Station, Texas, USA) was used to get the means, standard deviations, and interquartile ranges. Results were reported in frequency and percentage.

Results

In this study, we reviewed clinical files from patients who are HIV positive presenting with liver injury to the medical admissions ward at CHBAH. The demographics and baseline characteristics of these patients with abnormal liver function are depicted in table 1 and 2 below. The mean age was 43.7 in males and 39.9 in females.

Table 1: Demographics of patients in a cohort

Variable		95% CI	Males	95% CI	Females	95%

Age(years) mean (SD)	41.8(12.4)	40.1-43.5	43.7(11.5)	41.5-45.9	39.9(13.1)	37.3-42.5
Sex n(%)	208		105(50.5%)		103(49.5%)	

As shown in table 2 below, patients on ARVs made up 58% of the patients under the study and 88.4% (n=107), 10.7% (n=13) and 0.8% (n=1), were on 1st line, 2nd line and 3rd line respectively. The majority of patients on ARVs were females accounting for 55.3% (n=67) and males made up 44.6% (n=54).

The mean CD4 count was 273 cells/ul, with a mean CD4 count for males 218.2 and females 317.1 cells/ul, respectively. The viral load ranges from 0 copies per mil to 100 00000 copies/ml with a mean viral load of 429761.7 copies. Abnormal liver functions show a mean total bilirubin of 35.3, ALP of 226.7, GGT of 252, AST 174.2, ALT 103.2, and mean albumin of 29.72 and mean INR of 1.7. The mean of the GGT and ALP are higher than the transaminases, which may suggest obstructive or infiltrative patterns compared to hepatitic.

Table 2: Baseline characteristics of patients in a cohort

Variable		95% CI	Males	95% CI	Females	95% CI
ART regimen n(%)	121(58.1%)		54(44.6%)		67(55.4%)	
1st line n(%)	107(88.4%)		48(44.9%)		59(55%)	
2nd line n(%)	13(10.7%)		5(38.5%)		8(61.5%)	
3rd line n(%)	1(0.8%)		1(100%)		0(0%)	
CD4 count Mean (SD)	273.1(298.3)	218.5-327.7	218.2(248.4)	149.0-287.3	317.0(328.1)	225.7-351.0
Viral load Mean (SD)	429761.7(1352218)	234152.4-625370.6)	433395.1(1369645)	155879.2-710911	470443.1(1361006)	190147-750738.9
Total bili Mean (SD)	35.3(67.5)	26.1-44.6	28.2(56.1)	17.5-38.8	42.0(76.5)	27.0-56.9
Direct bili Mean (SD)	208(27.5)	19.9-35.1	20.6(43.3)	12.4-28.8	34.0(64.8)	21.4-46.7
ALP Mean (SD)	226.7(212.3)	197.7-255.8	223.2(177.6)	189.5-256.9	231.2(244.5)	183.5-279.0
GGT Mean (SD)	252.1(446.2)	190.9-313.3	196.9(201.8)	158.5-235.4	302.7(595.8)	186.3-419.2
AST Mean (SD)	174.2(313.2)	131.3-217.1	166.1(325.9)	104.0-228.3	181.3(295.2)	123.6-239.0
ALT Mean (SD)	103.2(248.4)	69.3-137.2	104.1(295.7)	46.5-156.8	102.4(190.0)	65.2-139.5
Albumin Mean (SD)	29.72(8.1)	28.6-30.9	29.2(8.0)	27.6-30.8	29.9(8.4)	28.2-31.5
INR Mean (SD)	1.7(1.7)	1.5-2.0	1.6(0.8)	1.3-1.8	1.9(1.6)	1.5-2.3

Patterns of liver injury found during this study were infiltrative, mixed, hepatocellular, and cholestatic. The patterns of liver injury are shown in table 3 below, with the most common

pattern found in the study being infiltrative, accounting for 67.8% (n=141) of all cases. Mixed pattern made up 22.1% (n=46), hepatocellular pattern at 7.7% (n=16) of the cases and the least common was cholestatic pattern with 2.4% (n=5) of the cases.

Table 3: Patterns of liver injury in a cohort

Patterns	Total (n)	Percentage (%)
Infiltrative	141	67.8
Mixed	46	22.1
Hepatitic	16	7.7
Cholestatic	5	2.4

Etiologies found in the study are depicted in table 4 below, with Mycobacterium tuberculosis (MTB) infection accounting for 36% (n=75) of all cases with abnormal liver enzymes, mycobacterium avian complex/mycobacterium other than tuberculosis, 2.8% (n=6), HBV infection, 6.2% (n=13), HCV infection, 0.4% (n=1), with non-Hodgkin lymphoma and Hodgkin lymphoma accounting for 6.2% (n=13) and 1.9% (n=4) cases respectively. Drug-induced liver injury (DILI) 5.7% (n=12), RVD cholangiopathy 1.4% (n=3), and other opportunistic infections (i.e., pneumocystis jiroveci pneumonia) 7.7% (n=16) were among etiologies found in this study. Other metastatic non-benign lesions 5.3% (n=11), Heart failure 4.8% (n=10), biliary masses 1.4% (n=3), Alcoholic liver disease 1.4% (n=3), Hepatocellular carcinoma 0.4% (n=1), and herbal toxicity 0.4% were also amongst etiologies ascribed by treating physicians. In 26.4% (n=55) of cases, the diagnosis was either unknown, or the treating physician ascribed no diagnosis.

The liver injury patterns in relation to etiologies are also depicted in table 4, with the infiltrative pattern found to be the most common, irrespective of the etiology. MTB infection accounted for 33.3% (n=47), HBV infection at 5.6% (n=8), HCV infection at 0.7% (n-1), mycobacterium other than tuberculosis at 4.2% (n=6) of the infiltrative pattern, with other opportunistic infections accounting for 9.2% (n=13), non-Hodgkin lymphoma at 7.8% (n=11), Hodgkin lymphoma at 1.4% (n=2), DILI made up 1.4% (n=2), hepatocellular carcinoma at 0.7% (n=1), other metastatic non-benign lesions at 7.8% (n=11), heart failure at 6.3%

(n=9), alcoholic liver disease at 1.4% (n=2) and non-alcoholic fatty liver disease, autoimmune hepatitis contributed 0.7% (n=1) each, of all infiltrative pattern cases.

With liver injury patterns, MTB was found in 33.3% (n=47), 43.4% (n=20), 43.7% (n=7), and 20% (n=1) of the infiltrative, mixed, hepatocellular, and cholestatic patterns respectively. HBV infection accounted for 5.6% (n=8) of infiltrative, 12.5% (n=2) of hepatocellular, and 4.3% (n=2) of mixed patterns. Non-Hodgkin lymphoma accounted for 7.8% (n=11) of infiltrative, 2.1% (n=1) mixed, and 6.2% (n=1) hepatocellular patterns. DILI accounted for 15.2% (n=7) of mixed, 1.4% (n=2) of infiltrative, 12.5% (n=2) of hepatocellular, and 20% (n=1) of the cholestatic patterns. RVD cholangiopathy made up 40% (n=2) cholestatic and 2.1% (n=1) of mixed patterns. Of the patients with DILI, 66.6%(n=8) were on antituberculosis therapy (rifampicin, isoniazid, ethambutol and pyrazinamide), with 16.6%(n=2) on 1st line ART (tenofovir, lamivudine and efavirenz), whilst the remainder had no known possible drug culprits.

A significant number of patients, 34.1% (n=71), contributed to at least one-third of patients in the study, wherein the diagnosis was either unknown or not directly related to the liver injury. Those were, Other opportunistic infections accounting for 7.7% (n=16), other diagnoses made up 13% (n=27), and no diagnosis at 13.4% (n=28).
The typical pattern in this group of patients was also infiltrative. Other opportunistic infections accounted for 9.2% (n=13) of infiltrative patterns, 12.5% (n=2) of hepatocellular patterns, and lastly 2.1% (n=1) of mixed patterns. Other diagnoses accounted for 14.1% (n=20) of infiltrative patterns, 13% (n=6) mixed patterns, and lastly, 6.2% (n=1) of cholestatic pattern. No diagnosis accounted for 12% (n=17) of infiltrative patterns, 17.4% (n=8) and 18.7% (n=3) of the cholestatic patterns.

Table 4: Percentages of patterns found in different etiologies

Etiology	Total n(%)	Infiltrative pattern n(%)	Mixed pattern n(%)	Hepatocellular pattern n(%)	Cholestatic pattern n(%)
MTB	75(36%)	47(33.3%)	20(43.4%)	7(43.7%)	1(20%)
No diagnosis	28(13.4%)	17(12%)	8(17.4%)	3(18.7%)	0(0%)
Other diagnoses	27(13%)	20(14.1%)	6(13%)	1(6.2%)	0(0%)
Other OI	16(7.7%)	13(9.2%)	1(2.1%)	2(12.5%)	0(0%)
HBV	13(6.2%)	8(5.6%)	2(4.3%)	2(12.5%)	1(20%)
NHL	13(6.2%)	11(7.8%)	1(2.1%)	1(6.2%)	00%)
DILI	12(5.7%)	2(1.4%)	7(15.2%)	2(12.5%)	1(20%)
Other metastatic NBL	11(5.3%)	11(7.8%)	0(0%)	0(0%)	0(0%)
Heart failure	10(4.8%)	9(6.3%)	1(2.1%)	0(0%)	0(0%)
MAC/MOTT	6(2.8%)	6(4.2%)	0(0%)	0(0%)	0(0%)
HL	4(1.9%)	2(1.4%)	2(4.3%)	0(0%)	0(0%)
RVD cholangiopathy	3(1.4%)	0(0%)	1(2.1%)	0(0%)	2(40%)
Biliary masses	3(1.4%)	0(0%)	2(4.3%)	0(0%)	1(20%)
ALD	3(1.4%)	2(1.4%)	1(2.1%)	0(0%)	0(0%)
HCV	1(0.4%)	1(0.7%)	0(0%)	0(0%)	0(0%)
NAFLD/NASH	1(0.4%)	1(0.7%)	0(0%)	0(0%)	0(0%)

Autoimmune hepatitis	1(0.4%)	1(0.7%)	0(0%)	0(0%)	0(0%)
Herbal toxicity	1(0.4%)	0(0%)	1(2.1%)	0(0%)	0(0%)
HCC	1(0.4%)	1(0.7%)	0(0%)	0(0%)	0(0%)

A total of 21.6% (n=45) of biopsies were done, as depicted in Table 5 below. Fifteen, 7.2% were bone marrow biopsies, 5.8% (n=12) liver biopsies, 4.3% (n=9) lymph node biopsies, 2.4% (n=5) lymph node fine needle aspirations (FNA), 0.9% (n=2) skin biopsies, 0.5% (n=1) colon biopsy and 0.5% (n=1) biliary biopsy. These results were used to assign possible etiology by treating physicians. However, apart from liver biopsy, the other biopsy results had no significant impact as confirmatory to the etiology of liver injury.

Table 5: Biopsy in a cohort

Biopsy	Total cases (n)	Percentage (%)
Bone marrow aspiration and biopsy	15	7.2
Liver biopsy	12	5.8
Lymph node biopsy	9	4.3
Lymph node FNA	5	2.4
Skin biopsy	2	0.9
Colon biopsy	1	0.5
Biliary biopsy	1	0.5
Total biopsies	45	21.6

Of the total 21.6% (n=45) of biopsies done, the liver biopsy contributed 5.8% (n=12), as shown in Table 6. Two, 16.6% of total liver biopsies done had features of steatohepatitis, with 16.6% (n=2) having features of metastatic non-benign lesions, 25.1% (n=3) with features of DILI and 16.6% (n=2) having features in keeping with RVD cholangiopathy, while 25.1% (n=3) of liver biopsies results were of unknown diagnosis

Table 6: Liver biopsy results features

Liver biopsy results	Total (n)	Percentage (%)
Steatohepatitis	2	16.6
Metastatic NBL	2	16.6
DILI	3	25.1
RVD cholangiopathy	2	16.6
Unknown	3	25.1

Discussion

This study demonstrated that liver injury is common in PLWHA in both males and females. The main problem with HIV and AIDS is immunosuppression. Consequently, those infected are at risk of multi-organ involvement, including liver injury from the HIV itself or various etiologies (10). Liver function tests measure synthetic, biliary, and intracellular functions. Abnormal LFTs are characterized by elevations above the upper limit of normal in ALT, AST, ALP, GGT, and bilirubin.

A study in Nigeria by Ejimele et al. found that 85.5% of their cases were classified as hepatocellular patterns (6). This differs from our study, which shows that the most common pattern of liver injury is an infiltrative pattern, then a mixed pattern, followed by a hepatocellular pattern, and lastly cholestatic pattern of liver injury. An infiltrative pattern in which the liver is invaded by a non-hepatic substance, often resulting in a liver injury similar to a cholestatic pattern with elevation in ALP and GGT, was the most common pattern in this study. A mixed pattern in which there is both cholestatic and hepatic enzyme, as well as elevation in bilirubin, was the second most common pattern of liver injury, followed by hepatocellular pattern, in which the primary injury is to the hepatocytes with elevation in ALT and AST with or without elevation in total bilirubin and lastly cholestatic pattern of injury in which injury is to the bile ducts with elevations in ALP and GGT, with or without elevations in Bilirubin and this was the least common pattern of liver injury.

Price et al., 2010 indicated in their study that the spectrum of liver disease shifted in the era of ART to concomitant HCV infection, HBV infection, DILI, alcohol abuse, and NAFLD (17), while Andotsakos et al., 2020 confirmed similar liver conditions in PLWHA. However,

in this study, MTB infection, HBV infection, lymphomas, MOTT, and DILI were among the significant groups implicated as causes of liver injury, with a large group of either unknown diagnosis or diagnosis not directly related to liver injury, 34.1% (n=71). Jha et al., 2017 implicated opportunistic infections as the cause of liver injuries with 6.2% (n=9) cases of tuberculosis infection and 5.6% (n=8) cases of HCV infection as a hepatocellular pattern in contrast to the findings of this study where MTB infection, MOTT, and HBV infections are the most common opportunistic infections found in PLWHA leading to majority infiltrative, then mixed, hepatocellular and cholestatic pattern of liver injuries (18).

In patients (PLWHA) presenting to CHBAH with liver injury, it is essential to recognize the pattern of liver injury bearing in mind the most common (infiltrative) with a high index of suspicion for MTB infection as it is the most common etiology of liver injury. Though it might differ from other parts of the world, in our study, MTB was the most common etiology of liver disease, with 33.3% (n=47) cases accounting for infiltrative pattern, 43,4% (n=20) accounting for mixed pattern, 43.7% (n=7) accounting for hepatocellular pattern, and last 20% (n=1) accounting for a cholestatic pattern of liver injury. Irrespective of the pattern of liver injury, MTB infection was found to be the most common etiology for liver injury in PLWHA at CHBAH at the time of this study. This is likely due to infiltration or replacement of the liver by a granulomatous process of MTB infection.

Though prior studies (13) in other parts of the world have found that drug-associated hepatotoxicity and viral hepatitides are the most common cause of liver disease in PLWHA, in this study, HBV infection accounted for only 6.2% (n=13) of all cases of liver injury. The typical pattern in HBV infection was also infiltrative. HCV infection accounted for only 0.7% (n=1) of the cases, leading to an infiltrative pattern.
This also shows that infections leading to liver disease in PLWHA present with an infiltrative pattern of liver injury. This is important to note when presented with PLWHA with abnormal liver enzymes at CHBAH.

Drug-induced liver injury (DILI) has also been implicated in several previous studies as one of the common etiologies of liver disease in PLWHA; however, in this study, DILI only contributed 5.7% (n=12) of cases mostly presenting as a mixed pattern of liver injury. Liver injuries may be because of anti-TB drugs and ARTs.

Liver biopsies remain the gold standard for diagnosing and staging liver fibrosis; however, 5.7% (n=12) of liver biopsies were performed in this study. Nine, 74.9% (n=9) of the liver biopsies were diagnostic, with three, 25.1% (n=3) diagnoses unknown. None of the liver biopsies done were diagnostic of MTB infection.

An audit done in the Gastroenterology department at CHBAH showed that histology was concordant with the diagnosis ascribed by the treating physician, posing the question, is it necessary?

Strength of the study

The study ascribes all patterns of liver injuries and recognizes the common etiology of PLWHA in the South African context where TB is endemic.

Limitations

Missing information due to the retrospective nature of the study. The study was conducted only at CHBAH, and most of our patients with TB and HIV are managed at the primary health care and district level.

Recommendation

All healthcare workers should be educated on the importance of screening all opportunistic infections and monitoring and managing liver abnormalities in PLWHA.

Conclusion

Liver injuries are common in PLWHA, with the infiltrative pattern being the most common and MTB being a common etiology. It is vital to screen opportunistic infections, including TB, HBV, and HCV, in PLWHA to prevent, monitor, and manage liver abnormalities to prevent mortality associated with the liver disease among PLWHA.

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Annexure 1: Ethics approval letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

27 April 2020

To Whom It May Concern

SUBJECT: **CONFIRMATION OF PROVISIONAL STUDY APPROVAL**
(This letter is not a clearance certificate - not yet cleared)
Protocol Ref No: M200315
Protocol Title: Patterns of liver injury in HIV positive patients in the medical admissions ward at Chris Hani Baragwanath Academic Hospital
Principal Investigator: Dr Rudzani Wendy Ndwambi et al
Department: Internal Medicine

This letter serves to confirm that the Human Research Ethics Committee (Medical) has granted provisional approval for the above mentioned study subject to receipt of written permission to do the study from the CEO of the study site and if required from the Gauteng Provincial Research Committee (GPRC).

Please note that this provisional approval letter does not permit data collection/secondary data analysis or any other form of research. Research may only be started when an applicant has received the final clearance certificate from the HREC (Medical) Secretariat.

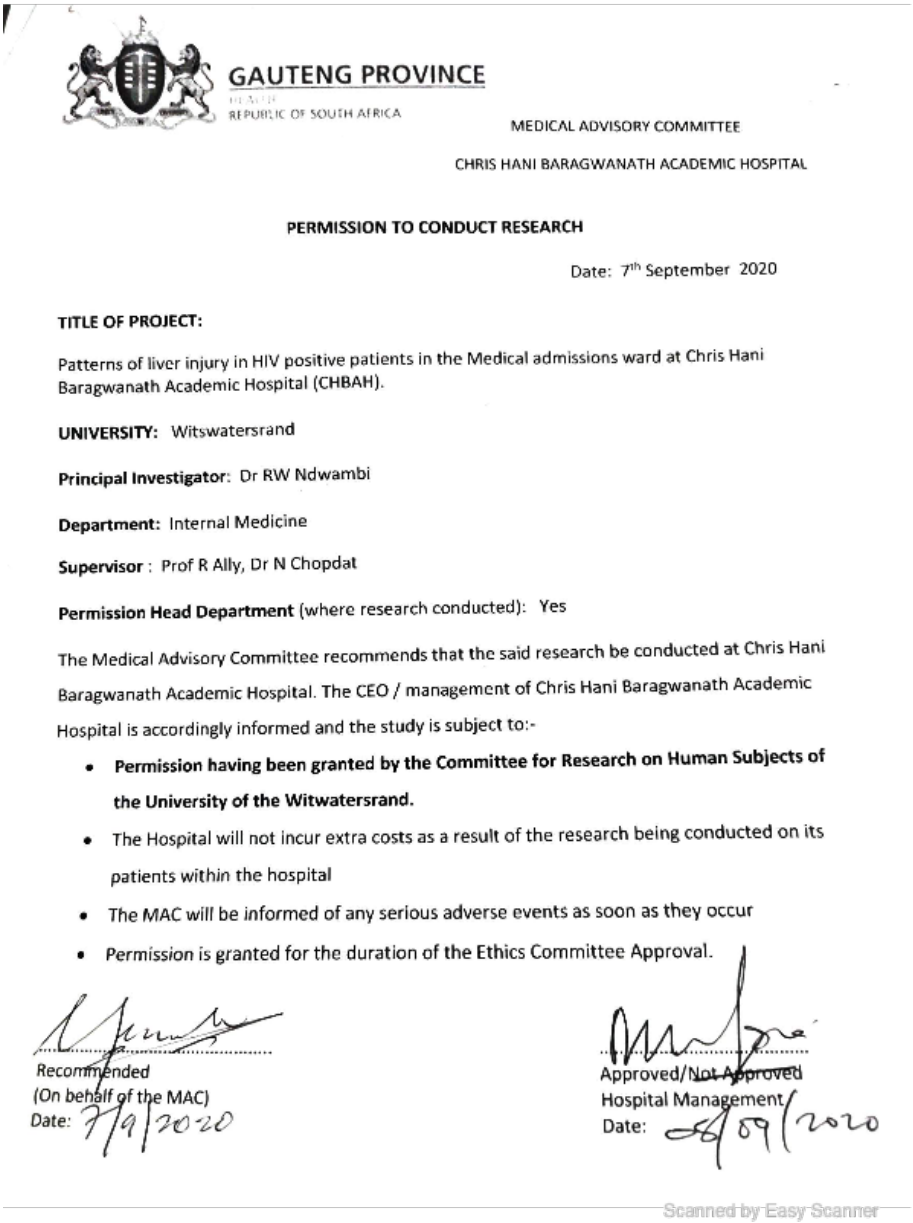
Should you have any queries, you may contact me at tel: 011 717 1234/2700/2656 or by email Mapula.Ramaila@wits.ac.za or HREC-Medical.ResearchOffice@wits.ac.za

Yours Faithfully,

Miss Mapula Ramaila
Administrative Officer
Human Research Ethics Committee (Medical)

Research Office Secretariat: Faculty of Health Sciences, Phillip Tobias Building, 3rd Floor, Office 304, Corner York Road and 29 Princess of Wales Terrace, Parktown, 2193 Private Bag 3, Wits 2050 I T+27 (0)11-717-1234/2656/2700/1252 E: Mapula.Ramaila@wits.ac.za I Office E HREC-Medical.ResearchOffice@wits.ac.za IWebsite: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

Annexure 2: Medical advisory committee approval letter



GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 7th September 2020

TITLE OF PROJECT:

Patterns of liver injury in HIV positive patients in the Medical admissions ward at Chris Hani Baragwanath Academic Hospital (CHBAH).

UNIVERSITY: Witswatersrand

Principal Investigator: Dr RW Ndwambi

Department: Internal Medicine

Supervisor : Prof R Ally, Dr N Chopdat

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 7/9/2020

Approved/Not Approved
Hospital Management
Date: 08/09/2020

Scanned by Easy Scanner

Annexure 3: Head of Department of internal medicine approval letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Chris Hani Baragwanath Academic Hospital
Department of Medicine
P.O. Bertsham
2013
Tel: +27 11 933 2040
Fax: +27 11 938 1454

25 August 2020

Dr JML Tsitsi
Head: Department of Internal Medicine
Chris Hani Baragwanath Academic Hospital

Dear Dr Tsitsi

re: **PERMISSION FOR DR RUDZANI WENDY NDWAMBI TO CONDUCT A MMED ENTITLED "PATTERNS OF LIVER INJURY IN HIV POSITIVE PATIENTS IN THE MEDICAL ADMISSIONS WARD AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL (CHBAH)"**

As one of the supervisors, I hereby request permission for Dr Rudzani Ndwambi, to conduct a MMed study at Chris Hani Baragwanath Academic Hospital. Title: Patterns of liver injury in HIV positive patients in the Medical admissions ward at Chris Hani Baragwanath Academic Hospital (CHBAH).

Permission will also be obtained for the University of the Witwatersrand Ethics Committee.

Thanking you in anticipation.

Yours sincerely

R Ally.

PROF. R. ALLY
Head: Division of Gastroenterology
Department of Medicine
Chris Hani Baragwanath Academic Hospital

Signature of approval by Dr Tsitsi – Head: Department of Medicine .....
Date 28/08/2020

Annexure 4: Data collection sheet

1. Data collection sheet	
Patient study number	
Age	
18-25	
26-35	
36-45	
46-55	
56-65	
66-75	
>75	
Gender	
M	
F	
ART	
Y	
N	
ART Regimen	
First line	
Second line	
Third line	
CD4 (cells/ul)	
Viral load (copies/ml)	
Risk factors:	
Preexisting liver disease (Y/N)	
Viral hepatitis	
NAFLD	
Autoimmune	
NBL	
other	
Comorbid disease (Y/N)	

TB	
Dyslipidaemia	
Other	
Comorbid treatment (Y/N)	
ATT	
Other	
Alcohol	
Mild	
Moderate	
Severe	
Other toxins	
Traditional medications	
Other	
Clinical presentation	
Jaundice	
Pruritus	
Changes in stool and urine colour	
Abdominal distension	
Liver failure	
Incidental	
Other	
Clinical examination findings	
Jaundice	
Hepatology	
Portal hypertension	
Liver failure	
Other	
Hepatic biochemistry	
LFTs ALT AST ALP	

INR	
Albumin	
Glucose	
Serological markers	
Hep BsAg P/N/U	
Hep C Ab P/N/U	
Hep E Ab P/N/U	
ANA P/N/U	
ALKM1 P/N/U	
Imaging (if available)	
Ultrasound Fatty liver Microabscesses Cirrhosis Portal HPT HCC Other	
CT scan abdomen Fatty liver Microabscesses Cirrhosis Portal HPT HCC Other	
MRCP Obstruction Dilated ducts Other	
Histology (if available)	