The incidence of, and risk factors for, liver injury in adults living with human immunodeficiency virus initiating antiretroviral therapy in a South African private sector managed care cohort

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Preamble

Declaration

I, Suniti Sinha, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 31 May 2023

Part A. The study protocol is presented here. It includes the background, rationale and methodology of the research done for this mini-dissertation.

Part B. A journal-ready manuscript according to the requirements of the Pharmacoepidemiology and Drug Safety journal .

Part C. All additional documentation necessary as supplementation in the presentation of this mini-dissertation.

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List of abbreviations

3xULN	Three times the upper limit of normal
5xULN	Five times the upper limit of normal
ADR	Adverse drug event
AfA	Aid for AIDS
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
Anti-TB	Anti-tuberculosis
ART	Antiretroviral therapy
DILI	Drug induced liver injury
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
ICD-10	International Classification of Diseases, 10th Revision
IQR	Interquartile range
IU/L	International units per litre
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
PI	Protease inhibitor
PLHIV	People living with HIV
OR	Odds ratio
TB	Tuberculosis
UCT	University of Cape Town
WHO	World Health Organization

Part A. Research Protocol

1. Synopsis

1.1 Background

People living with HIV (PLHIV) on antiretroviral therapy (ART) are at risk for liver injuries. Previous studies have described the risk of drug-induced liver injury (DILI), but data regarding incidence of hospitalisations due to liver injury are limited.

1.2 Purpose and objective of the study

Primary aim: To estimate the incidence of, and risk factors for, liver injury in PLHIV initiating ART enrolled in the Aid for AIDS (AfA) private sector cohort.
Secondary aim: To estimate the incidence of, and risk factors for, hospital admissions due to liver injury in PLHIV initiating ART enrolled in the AfA cohort.

1.3 Methodology

We conducted a retrospective cohort analysis using data from an HIV disease management programme of medically insured South African patients, AfA. We defined liver injury as alanine aminotransferase (ALT) concentrations at least three times the upper limit of normal (3xULN), and severe liver injury as those with ALT levels of at least five times the upper limit of normal (5xULN), where ULN was 40 IU/L. We estimated the incidence of hospital admissions due to liver injury and explored potential risk factors (including age, viral load and CD4 count at ART initiation, sex, ART regimen, alcohol-induced pathology, and being on anti-TB drugs), using Kaplan Meier estimates to describe the incidence of, and Cox regression to assess associations with, first liver injury episode (ALT $\geq$ 120 IU/L and ALT $\geq$ 200 IU/L), as well as first hospital admission associated with liver injury (ALT $\geq$ 120 IU/L and ALT $\geq$ 200 IU/L).

1.4 Study population

We included adult PLHIV (aged > 18 years old) with detectable HIV viral loads at the time of first documented ART initiation (assumed to be antiretroviral-naïve). We excluded PLHIV with suppressed viral loads at the point of enrolment into the cohort.

1.5 Recruitment and enrolment

We used secondary data, comprising a database of medically insured South African PLHIV. We included all patients who met the inclusion criteria.

1.6 Benefits of the study

Information regarding incidence and risk factors for liver injury and liver injury associated with hospitalisations may improve routine HIV care by identifying which patients may require more stringent monitoring.

1.7 Risks of the study

The data collected for this analysis was part of a routine database based on medical aid claims. The analysis was retrospective, so it did not impact the clinical care of included subjects. Patient identifiers were not included and not available to investigators. We reported aggregate results only. Thus, the potential probability and severity of foreseeable harm for study subjects was minimal and not clinical in nature.

1.8 Informed consent process

An informed consent process was not applicable in this study. Previous University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee (HREC) approval was received, allowing AfA to collect anonymised data to be used for observational analyses (HREC REF: 858/2016, as renewed annually). The UCT Faculty of Health Sciences HREC also approved this analysis (HREC ref 824/2019, as renewed annually).

1.9 Privacy and confidentiality

The database comprised anonymous patient information only. There was no identifying information, thus protecting participants’ privacy. In addition, the investigators kept all data confidential.

2. Background

2.1 Introduction

Antiretroviral treatment (ART) has converted Human Immunodeficiency Virus-1 (HIV-1) from what was once a fatal disease to a manageable chronic condition, by reducing mortality and associated morbidity. Despite the fact that more people are living longer with HIV-1 infection now due to ART, more are presenting with adverse drug reactions (ADRs) (1). Drug-induced-liver injury (DILI) is one of the more common ADRs, and is associated with being antiretroviral-naïve, taking a regimen that contains non-nucleoside reverse transcriptase inhibitors (NNRTIs) and/or protease inhibitors (PIs) (2–6), Hepatitis B (HBV) and/or Hepatitis C (HCV) co-infection, baseline increases in alanine transaminase (ALT) level, being on anti-tuberculosis (anti-TB) drugs, pre-existing hepatic dysfunction or chronic liver disorders have also been associated with developing DILI (1–3,7). Being female and older age have had inconsistent associations with DILI reported, along with whether a high CD4 cell count or low CD4 count pre-treatment is associated with DILI (3,4,6–13). DILI is a spectrum of liver toxicities that range from transient elevations in transaminases to liver failure, and sometimes may be fatal (1). Given the large proportion of South Africans who are on long term ART, DILI is likely to remain a significant burden for some time. While hospital surveys have given us important insights into potential risk factors for DILI-related hospital admissions, to our knowledge, no studies have provided accurate denominator data for estimating incidence.

The aim of this study was to investigate the incidence of liver injury and liver injury-related hospital admissions in a South African cohort of PLHIV on ART. We performed a retrospective cohort analysis using routine clinical data from Aid for AIDS (AfA), a large private sector HIV disease management programme in Southern Africa with a large denominator.

2.2 Definition of liver injury in PLHIV on ART

Suspected cases of DILI are, by definition, drug-related, herbal-related, or dietary supplement-related liver injury, and are recognized by abnormal liver biochemical markers with or without clinical manifestation (14). Different studies identify liver injury in PLHIV or those on anti-TB treatment through a variety of definitions that take into account biochemical markers and/or clinical symptoms. However, a widely accepted definition is to use elevated ALT levels (a common marker to determine liver injury) that is proposed by the Division of AIDS (which is part of the United States' National Institutes of Health's National Institute of Allergy and Infectious Diseases) and is specifically used as a grading system that was designed for use in network clinical trials about liver injury (15):

- Grade 1 (mild): 1.25 – <2 x ULN
- Grade 2 (moderate): 2.5 – 5.0 x ULN
- Grade 3 (severe): 5.0 – 10.0 x ULN
- Grade 4 (potentially life threatening): ≥ 10.0 x ULN

In our setting, the normal reference range for ALT is 1 – 40 IU/L (16).

2.3 Incidence of liver injury and incidence of liver injury-related hospitalisations in PLHIV in South Africa

DILI occurs in 9-30% of PLHIV on treatment, depending on the setting and definition used (17). These are global estimates from before universal ART was recommended by the World Health Organization in 2015 (18). In South Africa, studies done before universal ART implementation have estimated incidence of DILI, as defined by ALT≥200 IU/L, as 0.26-17% in cohorts of less than 3 800 PLHIV (19–21). Since the implementation of universal ART, local data on DILI in PLHIV in South Africa not on first-line anti-TB treatment is limited. One randomised controlled trial published in 2020 was conducted at the Centre for the AIDS Programme of Research in South Africa eThekwini treatment clinic in PLHIV co-infected with TB looking at how the risk of liver injury varied according to when ART was started on co-infected TB/HIV patients already on TB treatment (22). This study defined liver injury as an elevated ALT of grade 1 or more, and found that amongst PLHIV on TB treatment with normal baseline liver enzymes, 34%, 30% and 29% developed liver injury when starting ART early, late into TB treatment, and after TB treatment, respectively (22). This showed us that despite being in the era of universal ART, the incidence of liver injury is crucial to monitor in HIV/TB co-infected patients.

To our knowledge, no previous studies in South Africa have reported the incidence of liver injury-related hospitalisations. However, hospital survey data has given us some idea of the proportion of a given number of hospital admissions that are due to liver injury in PLHIV on ART in our setting, as well as identifying potential risk factors, and describing outcomes. In Johannesburg a retrospective study found that of the PLHIV that were hospitalised with DILI, 35.7% had anti-TB drug associated DILI, 22.5% had ART-associated DILI and 41.9% had mixed anti-TB drugs and ART-associated DILI (23). A similar hospital study done in Cape Town showed that 71 of 318 (22.3%) hospitalised PLHIV with significant liver dysfunction had anti-TB drugs or ART-associated DILI, whereas another Cape Town study showed that of 162 adverse event admissions, 50% were attributable to anti-TB drugs and 28% to the use of nevirapine (24,25). In addition, a cross-sectional study done in 4 hospitals in South Africa showed that liver injury was one of the most common ADR-related admissions, where 56 of 164 of patients admitted with ADRs were on ART or anti-TB therapy and of these DILI cases, 90% were in PLHIV (26). Another study done in Cape Town looked at the distribution of ADRs in adult medical inpatients (not all HIV positive) and found that hepatobiliary toxicity was the third most prevalent ADR, where 10 out of 16 patients were admitted due to liver injury from anti-TB drugs (27).

These perspectives from various public sector hospitals give us some idea of the data available on the proportion of hospital admissions that are due to ADRs in South Africa and highlight the burden of anti-TB drugs and/or ART-associated DILI, but do not inform us of the incidence as a large population denominator was not used.

In comparison, other developing countries like South Africa have shared similar findings of the importance of anti-TB drugs in liver injury in PLHIV on ART. A study in Brazil of 149 hospitalized PLHIV (of which 65 were ART-naïve), showed that 19.6% were using potentially hepatotoxic drugs prior to admission, largely first line anti-TB drugs (10).

2.4 Antiretrovirals associated with liver injury

ART is the treatment of choice for PLHIV and is indicated as lifelong therapy. Thus, any toxicity caused by these drugs becomes important in the management of these patients, and determining their adherence to the prescribed therapeutic regimen (13). Of all antiretroviral drugs available, a few have been shown to be strongly associated with liver injury. Although no longer recommended as the first line ART regimen in current guidelines (28), those on nevirapine are more likely to experience any grade of liver injury (Odds ratio (OR) 1.5, 95% CI 1.3–1.8) or severe liver injury (as defined by ALT levels of 5.0 – 10.0 x ULN) (OR 3.3, 95% CI 2.5–4.2) compared to those on efavirenz (7,29–31). Hepatotoxicity from use of efavirenz is also recognised, but is reported to occur at a frequency far less that is seen with the use of nevirapine (32).

An earlier clinical trial was conducted in Germany from July 1998 to December 2001 which included 296 PLHIV of whom 151 were on efavirenz and 145 on nevirapine (3). The overall rate of severe hepatotoxicity (grade 3 to 4 elevations in aspartate aminotransferase and/or alanine aminotransferase) was 2 of 151 (1.3%) in patients prescribed efavirenz and 3 of 145 (2.1%) in patients prescribed nevirapine (3). Mild-to-moderate hepatotoxicity (grade 2 elevation) was observed in 6.0% (efavirenz) and 3.4% (nevirapine) of patients (3). However, more recent observational studies estimate the incidence to be slightly higher as 1-8% in PLHIV on efavirenz have ALT> five times ULN (33).

Patients who take PIs have also been observed to be at increased risk of liver injuries (34). Additionally, another study found hyperbilirubinemia to occur in patients taking indinavir (34) was associated with a higher incidence of elevated liver enzymes versus other PIs after the first 6 months of antiretroviral therapy – 14 of 680 indinavir users (2.1%) versus 2 of 645 patients (0.3%) receiving other antiretroviral drugs (p=0.003) (34). Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are used frequently as part of antiretroviral regimens, and so their potential to also cause liver injury should be kept in mind (35). Patients on NRTIs may develop liver injury due to mitochondrial toxicity which results in lactic acidosis that has been observed in patients on both single or dual NRTI regimens– examples include stavudine, didanosine, and zalcitabine (all of which are no longer recommended in the 2023 South African National Department of Health guidelines) (28,36). Tenofovir may also induce mitochondrial injury when combined with other NRTIs, but the pathophysiological mechanism is not entirely understood (37). Abacavir is known to result in hypersensitivity reactions sometimes accompanied by elevations in liver enzymes or liver failure (14).

2.5 Liver injury in patients on concomitant antiretroviral therapy and TB treatment

First-line anti-TB drugs associated with liver injury include rifampicin, isoniazid and pyrazinamide. There is a high prevalence of both HIV and tuberculosis (TB) in South Africa (38).TB and HIV are inextricably linked. It should be noted that not only do PLHIV have a 30 times higher likelihood of developing TB in their lifetime, but they also have a higher risk of dying from TB than those that are not infected (39). It has been reported that an estimated 60-80% of new TB cases in South Africa are also HIV co-infected, and TB-DILI arising from first-line anti-TB drugs is estimated to affect 5-33% of TB patients (38). Due to South Africa being burdened by high rates of this dual disease phenomenon, it is imperative that we be aware that anti-TB drug associated DILI in PLHIV can complicate therapy, potentially affecting treatment adherence, leading to interruption of treatment and thus contributing to unfavourable outcomes (23,39,40).

2.6 Other risk factors for liver injury in PLHIV on ART

Aside from being on anti-TB drugs or on specific antiretrovirals as highlighted above, other studies have tried to identify potential risk factors associated with elevated ALT in patients on antiretroviral drugs. Raised ALTs have been found in patients who are co-infected with HBV and HCV (3,41,42). Studies have shown that HCV co-infection increases the risk of developing increases in liver enzymes by 2-7 fold in PLHIV on ART (4,6,8,9,13).

Another risk factor is a pre-existing elevated baseline ALT concentration, pre-existing hepatic dysfunction or chronic liver disorders (2,3,31,34). However, concurrent hepatobiliary disorders do not represent a contraindication to NNRTI use, but strict monitoring is recommended (31).

Alcohol is also a risk factor, and it is hypothesised that the raised ALTs are due to direct hepatocellular damage caused by the alcohol (41,42).

There are contradicting reports on whether sex is a strong risk factor; some studies have found an association with being female (2–4,6), while others have not found it to be a determining factor for having elevated ALTs, possibly due to the fact that the course of HIV progression and drug metabolism is not generally different in both sexes (21,41–45).

Results of studies have also been mixed with regards to age being a significant risk factor; some found that it is not a determinant factor for liver enzyme increases in those taking antiretrovirals (42,46,47). However, this could be because patients were mostly younger than 50 years of age, as there are also studies which found that being over 50 years of age is a risk factor (2–6,48).

Other risk factors that have been implicated include being ART-naïve (when PLHIV have never initiated treatment before, usually amongst those who are newly diagnosed), and being on certain ART regimens - as described above (2–4,6). A high CD4 cell pre-treatment has also been associated with severe hepatotoxicity, women with CD4 > 250 cells/mm^3 and men with CD4 > 400 cells/mm^3, potentially representing immune-mediated liver injuries (3,12). Some studies reported increases in CD4 of more than 50 cells/mm^3 during therapy to be associated with NNRTI-induced liver toxicity (4,6), but not many studies have confirmed this (4,6–9,13). However, it has also been shown that a high CD4 count can be protective against liver injury. One study in 2022 showed that there is a higher risk of ALT$\geq$ 200 IU/L if one's CD4 count is <200 cells/mm^3, and another was conducted in hospitalised PLHIV where those with CD4 >100 cells/mm^3 had half the likelihood to have liver injury than those with a CD4 <100 cells/mm^3 (10,11). Detectable viral load has been associated with a greater rate at which apoptosis and necro-inflammatory activity occurs, which can raise liver enzymes (41,42,49).

2.7 Other risk factors for liver injury-related hospitalisations

The cross-sectional study at 4 hospitals in South Africa described above reported that being female, having a greater pill burden (mostly with rifampicin or efavirenz), greater number of co-morbidities as well as being HIV positive on ART were all associated with being admitted with hepatotoxicity (26). Another study done in South Africa in 2008 found that of those admitted due to hepatotoxicity (n=16), 10 were due to anti-TB drugs and 1 was due to efavirenz (27). Risk factors that were associated with an ADR admission, included being of older age compared to those not admitted with an ADR (median age=53, interquartile range (IQR)=35-73 vs 42; IQR 30-60, p=0.003), and being HIV positive on ART made patients 10 times more likely to be admitted with an ADR compared to those not on ART (27).

2.8 ART regimens in PLHIV in AfA during the study period

PLHIV in our study were managed according to AfA treatment guidelines. The AfA clinical guidelines 10th edition was published in 2014, and recommended tenofovir/zidovudine, emtricitabine/lamivudine, and an NNRTI – either efavirenz or nevirapine – as first-line regimen (50). The 11th edition published in 2016 updated their first-line regimen to tenofovir/abacavir/zidovudine, emtricitabine/lamivudine, and an NNRTI – either efavirenz or rilpivirine (51)

2.9 Guidelines for ART eligibility and monitoring hepatoxicity from ART in PLHIV

One of the key differences between the AfA guidelines published in 2004 (10th edition) and 2016 (11th edition) was patient eligibility for initiating ART. The 2016 AfA guidelines were in line with the rollout of universal ART that was adopted by the South African National Department of Health and stated that anyone who tested positive for HIV regardless of CD4 count and disease staging, was eligible to start ART immediately (52). Universal ART was implemented into national guidelines for the public sector on 1 September 2016 (53).

However, the guidelines for monitoring hepatotoxicity from ART in PLHIV have remained the same. According to both the 10th and 11th edition of the AfA guidelines, it was recommended that only ALT be monitored in PLHIV with suspected DILI, as it is both a specific and sensitive indicator for DILI, but the full liver function test profile should be requested in patients who are symptomatic, suggestive of hepatitis with an ALT≥120 IU/L (51). The guidelines recommended that those who start nevirapine should have their ALT monitored at 2 weeks, 4 weeks, 8 weeks, 12 weeks, 6 months and 6-monthly thereafter (51). Furthermore, it was recommended that those with an ALT≥200 IU/L should have any potentially hepatotoxic drugs stopped, and if there are symptoms of hepatitis (eg right upper quadrant pain, jaundice, anorexia, nausea, vomiting) then the hepatotoxic drug should be stopped even if liver enzymes are <200 IU/L (51) .

3. Information gaps

1. There is limited data regarding the incidence of liver injury from real-life settings of PLHIV who were followed up after implementation of universal ART.
2. Hospital surveys have largely been used to report on ADRs as a proportion of hospital admissions, along with exploring associated risk factors to some extent, but to our knowledge there are no studies with an accurate denominator to estimate the incidence of liver injury-related hospitalisations in PLHIV on ART.

4. Purpose of the study

4.1 Aims

To estimate the incidence of, and risk factors for, developing liver injuries and hospitalisations associated with liver injuries, in PLHIV initiating ART enrolled in the AfA cohort in South Africa.

4.2 Objectives

In adult patients initiating ART in the AfA observational cohort, we will:

- Estimate the incidence of ALT concentrations 3xULN
- Estimate the incidence of ALT concentrations 5xULN
- Explore the associations between potential risk factors and developing liver injuries (as defined by elevated ALT concentrations)
- Estimate the incidence of hospital admissions associated with liver injuries
- Explore the associations between potential risk factors and hospital admissions associated with liver injuries

5. Methodology

5.1 Context

The analysis was conducted using data from the largest private sector HIV disease management programme in South Africa, Aid for AIDS (AfA). AfA initiated an antiretroviral programme in 1998, and in the last two decades has grown to include more than 100 000 patients from 9 countries in Southern Africa. Those enrolled in the AfA programme in South Africa are managed according to the AfA standard guidelines, largely based on the South African National Department of Health standard public sector guidelines (51,53). Data that was extracted from their database was CD4 count, viral load, age, sex, ART regimens, hospital admission ICD10 codes and drug claims. AST and ALT were the only laboratory data available on liver injury, but ALT was used as it is a specific and sensitive indicator for DILI (51,53).

5.2 Study design

This was a retrospective cohort study.

5.3 Time frame

We included patients in the AfA registry, included data regarding hospital admissions, from January 2011 to September 2018.

5.4 Characteristics of the study population

All records of patients registered in the AfA database are anonymised. We included all patients that fit the inclusion and exclusion criteria, as per below.

Inclusion criteria

1. Adults (18 years or older)
2. Patients that are newly started on ART ie. antiretroviral naïve prior to selected time frame of study. We defined a patient to be initiating ART if they were documented as ART naïve, and had unsuppressed viral loads, at the time of entry into the cohort

Exclusion criteria

1. Patients with suppressed viral loads at date of first documented ART initiation in AfA

5.5 Sample size

We included all patients who met the inclusion criteria and who had the necessary data available.

5.6 Definition of terms used in this study

This study made use of terms with definitions specific to the parameters of this study, having accounted for no misinterpretations and within the recognised limitations in this study, as well as no presumed notions regarding causality that may be attached with the below terms.

Antiretroviral regimens

We divided antiretroviral exposure into efavirenz-based, nevirapine-based, PI-based ART regimens (usually comprising 2 NRTIs plus the drug of interest) or "other". We excluded PLHIV who were flagged as being on ART but who had no ART records in the database.

Liver injury

We defined liver injury as an ALT ≥120 IU/L (ie. three times the upper limit of normal in our setting). The subset of individuals with ALT ≥200 IU/L (ie. five times the upper limit of normal) were defined as having severe liver injury. The term "liver injury" does not imply a causal relationship with antiretrovirals or other drugs.

Liver injury related hospitalisations

We defined liver injury-related hospitalisations as hospital admissions that occurred 3 days before or within 1 week after an elevated ALT (as defined by both ALT ≥120IU/L and ALT ≥200IU/L), with an International Classification of Diseases, Tenth Revision (ICD10) code that suggested liver injury. We excluded hospital admissions with an ICD10 code that indicated other non-drug-related causes of hepatitis (for example infectious, chronic, alcoholic, or autoimmune diseases).

Anti-TB drug exposure

We identified PLHIV as receiving anti-TB drugs if they claimed for rifampicin-containing anti-TB treatment or prophylaxis or had a documented TB-related hospital admission, based on ICD10 codes. We assumed that their TB treatment or prophylaxis period was up until 6 months from their first medicine claim for anti-TB medications or their first TB-related hospital admission (whichever came first).

Alcohol-related pathology

Patients were categorised as having alcohol-induced pathology if they had one or more ICD10 codes for alcohol-related admissions at any point during their follow up time. We were unfortunately unable to describe alcohol use in general as the database did not record this information directly.

6. Recruitment and enrolment

We used secondary data, from a database of a cohort of medically insured South African PLHIV from 2011 to 2018. No personal recruitment of patients was done.

7. Data collection and data management

We obtained the following data from AfA:

- Age
- Sex
- CD4 count
- Viral load
- ALT
- ART prescription data
- Hospital admission dates with an attached ICD10 code (ie the diagnosis at admission)

Data management

- We cleaned the data and excluded people with missing dates, missing CD4 or VL values, as well as missing ART regimen.
- We defined CD4 at ART initiation as the CD4 count closest to the patient's ART initiation date given that it is within a year before and 3 months after ART initiation date. We defined viral load at ART initiation by initially excluding those with viral loads <20 copies/ml, after which we sought out the viral load closest to the patient's ART initiation date given that it is within a year before and 3 months after ART initiation date.
- We generated the variable of anti-tuberculosis drug exposure as per above.
- We generated the four outcome variables as follows: ALT≥120 IU/L, ALT≥200 IU/L, a liver injury-related hospitalisation (ICD10 code) with an admission date that occurred within 3 days before or within 1 week after an ALT≥120 IU/L, or a liver injury-related hospitalisation (ICD10 code) with an admission date that occurred within 3 days before or within 1 week after an ALT≥200 IU/L.

8. Statistical analysis

We analysed data using Stata/SE version 15.0. We used descriptive statistics to describe and summarise the data obtained. We summarised age, CD4 count and viral load at ART initiation using medians and interquartile ranges (IQRs). We summarized categorical variables as frequencies (%). We used Kaplan Meier estimates to describe incidence of, and Cox regression to assess associations with, first liver injury episode (ALT $\geq$ 120 IU/L and ALT $\geq$ 200 IU/L), as well as first hospital admission associated with liver injury (ALT $\geq$ 120 IU/L and ALT $\geq$ 200 IU/L). We included *a priori* variables into the final multivariate cox proportional hazards model, including age, sex, CD4 count at ART initiation, viral load at ART initiation, antiretroviral regimen, alcohol-use pathology, and those on co-prescribed TB medication (for prophylaxis or treatment). We expressed the outcomes of getting a liver injury or having a liver injury-related hospitalisation as incidences per 100 person-years. We presented all hazard ratios with 95% confidence intervals, and p-values were considered significant at $p<0.05$. PLHIV were right censored if they died, or stopped and/or switched their initial ART regimen. Those who stopped or switched ART regimens were censored 7 days after the date of their stop or switch date, to incorporate anyone who may have discontinued their ART regimen because of signs and symptoms of liver injury. PLHIV were also right censored if they transferred out the cohort or at database closure (5th September 2018). We used tables and graphs to visually display the data.

9. Ethical considerations

In this study, we aimed to abide by the ethical principles of health research that includes justice, beneficence, and autonomy. This study sought and obtained approval from University of Cape Town Human (UCT) Faculty of Health Sciences (FHS) Human Research Ethics Committee (HREC) (Ref: 824/2019, as renewed annually). A previous approval allowing for AfA to collect anonymised data to use for observational analyses was also given by UCT's FHS HREC (HREC REF: 858/2016, as renewed annually).

9.1 Benefits of the study

In this study, we aimed to describe the incidence of liver injuries in PLHIV on ART enrolled in a large cohort with detailed data regarding hospital admissions, allowing us to determine the incidences of both raised ALT and hospitalisations thereof. The information gained through this study will contribute to understanding the burden of liver injury and liver injury-related hospitalisations in our large study cohort. Information regarding risk factors found to be associated with both liver injuries and hospitalisations thereof can give healthcare practitioners an idea of which patients may require more stringent monitoring when it comes to their routine care.

9.2 Risks of the study

The data collected for this analysis was part of a routine patient enrolment database based on medical aid claims, and our retrospective analysis had no impact on the clinical care of included patients. Patient identifiers were not included and were not available to investigators. Thus, the potential harm for study subjects was minimal (essentially negligible) and not clinical in nature, thus adhering to the ethical principle of non-maleficence.

9.3 Informed consent process

We did not need to seek informed consent. This was a retrospective analysis of routinely collected clinical, anonymised data. AfA has HREC approval to collect and store data for analysis.

9.4 Privacy and confidentiality

The AfA database was made up of patient information already in an anonymised form. Study participants were not able to be traced back as there was no identifying information, thus ensuring their safety and protection of their privacy. In addition, we were able to keep all data confidential and only presented aggregate results.

9.5 Dissemination of study results

The findings of this study will be available and accessible to researchers in the field of both pharmacology and infectious diseases by publishing the results in a peer-reviewed journal in the form of a manuscript, as well as presenting the findings at the third annual conference in pharmacoepidemiology that will be held 5-9 June 2023 in Cape Town, South Africa.

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Part B. Journal Manuscript

The incidence of, and risk factors for, liver injury in adults living with HIV in a South African private sector managed care cohort

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1. Abstract

Introduction

Hospital surveys found that drug-induced liver injury is a leading adverse reaction resulting in hospitalization and death in people living with HIV (PLHIV) in South Africa.

Objectives

To determine incidence of, and risk factors for, liver injury and liver injury-related hospitalizations in PLHIV on antiretroviral treatment (ART).

Methods

We described the incidence of, and associations with, ALT≥120 IU/L, ALT≥200 IU/L, and hospitalizations with raised ALT in PLHIV aged >18 years in the Aid for AIDS private sector cohort (comprising medical scheme beneficiaries) commencing ART between 2011–2018.

Results

We included 92,757 PLHIV; median age was 38.4 years; 42.5% were male, and 88.6% were on efavirenz-based ART. Incidence per 100 person years (95% confidence interval (CI)) of ALT≥120IU/L, ALT≥200IU/L, hospitalization with ALT≥120IU/L, and hospitalization with ALT≥200IU/L was 0.93 (0.89–0.97), 0.38 (0.36–0.41), 0.06 (0.05–0.07), and 0.04 (0.03–0.05), respectively. Adjusted hazard ratios (aHRs) (95% CI) for ALT≥120IU/L and hospitalization with ALT≥120IU/L respectively were 15.3 (12.1–19.3) and 6.27 (3.11–12.6) for antituberculosis drug exposure; 1.63 (1.31–2.02) and 1.50 (0.70–3.20) for efavirenz; and 2.74 (2.04–3.69) and 3.48 (1.24–9.73) for nevirapine, compared to protease inhibitors. AHRs (95%CI) for ALT≥200IU/L and hospitalization with ALT≥200IU/L respectively were 12.6 (9.31–17.1) and 5.68 (2.58–12.5) for antituberculosis drug exposure; 1.74 (1.28–2.37) and 1.97 (0.69–5.58) for efavirenz; and 3.01 (1.97–4.61) and 3.56 (0.93–13.65) for nevirapine. All HRs are adjusted for age, sex, CD4 count and viral load at ART initiation, and alcohol-induced pathology.

Conclusions

Exposure to antituberculosis drugs was strongly associated with liver injury. Safer anti-tuberculosis treatment regimens are needed for PLHIV.

2. 5 key points

Keywords

HIV, ART, liver injury, anti-TB drugs, hospitalizations, risk factors, South Africa

Key points

1. Hospital surveys report ART and anti-TB drugs as potential risk factors for liver injury, but the incidence of liver injury-related hospitalizations in PLHIV on ART is unknown
2. We found that the incidence of ALT ≥120 IU/L was lower than previous older studies
3. The incidence of hospitalizations with ALT ≥120 IU/L was fifteen-fold lower than the incidence of ALT≥120IU/L.
4. The use of anti-TB drugs was found to be the strongest predictor, followed by use of nevirapine and efavirenz, for liver injury and liver injury-related hospitalizations
5. PLHIV on ART need safer anti-TB drugs

3. Plain Language Summary

People living with HIV (PLHIV) on antiretroviral therapy (ART) are at risk of developing side effects resulting from the use of ART itself or the use of drugs to treat or prevent other HIV-associated diseases.

Drugs can cause damage to many organ systems throughout the body; the liver being one of the most commonly affected organs. Some drugs are more harmful than others; an awareness of this together with close monitoring of patients using these drugs is of utmost importance to prevent worsening disease and death.

This study identified how many PLHIV suffered liver injuries while on ART and examined if any other patient factors, such as other drugs they may be taking for other diseases, may have contributed to this. Interestingly, the overall number of patients who developed liver injuries in our study was lower than that reported in older studies, when different drugs were used, and PLHIV started ART later in the course of their HIV disease, when their immune systems were already weakened.

Receiving treatment for TB was the strongest risk factor for liver injury and liver injury-related hospitalizations. Thus, there is a need to ensure that PLHIV on ART are able to use safer TB treatment.

1. Introduction

Antiretroviral treatment (ART) is the definitive treatment for people living with HIV (PLHIV); and is indicated as lifelong therapy. Adverse events associated with the use of these drugs are not uncommon, and can exacerbate patient morbidity, resulting in poorer treatment outcomes largely due to their resulting poor treatment adherence (1). Additionally, and indeed commonly, PLHIV may be using other drugs for the treatment and prophylaxis of HIV-associated diseases, each associated with their own adverse event profile. Drug-induced liver injury (DILI) is a well described adverse drug reaction (ADR) in PLHIV in the South African populations (2).

Depending on the ART regimen in use and how DILI is defined in various studies, DILI is reported in 9-30% of PLHIV on ART (1). These are global estimates that predate the implementation of universal ART (ART eligibility regardless of CD4 count) as recommended by the World Health Organization (WHO) in 2015 (3). In South Africa, estimates of the incidence of ALT≥200 IU/L differ, ranging from 0.26 - 17%. Again, those studies were all conducted before universal ART in cohorts of fewer than 3 800 PLHIV (4–6).

Risk factors for ART-associated DILI in PLHIV that have been identified thus far include the use of antiretrovirals such as nevirapine, efavirenz and protease inhibitors (PIs), as well as being on first line anti-tuberculosis (anti-TB) drugs, co-infection with hepatitis C and/or hepatitis B (HCV and/or HBV), alcohol use, pre-existing elevated baseline ALT levels, pre-existing hepatic dysfunction, and chronic liver disease. Sex, age and CD4 count have shown inconsistent associations (2,4,7–32). Since the implementation of universal ART, data on DILI in PLHIV are limited in South Africa.

To our knowledge, the incidence of liver injury-related hospitalizations has not been estimated previously in South Africa. However, hospital surveys have shown anti-TB drugs and ART to be potential risk factors for DILI. In Johannesburg a retrospective study found that of those hospitalized with DILI, 35.7% had anti-TB drugs associated-DILI, 22.5% had ART-DILI and 41.9% had mixed anti-TB drugs or ART associated DILI (2). Similar work conducted in

Cape Town classified 71 of 318 hospitalized PLHIV with significant liver dysfunction were classified as anti-TB drugs or ART-associated DILI. This was further supported by a later study in Cape Town which showed that of 162 adverse event admissions, 50% were attributable to anti-TB drugs and 28% to the use of nevirapine (33,34). In addition, a cross-sectional study done in 4 hospitals in South Africa showed that liver injury was one of the most common ADR-related admissions, where 56 of 164 patients were on ART or anti-TB therapy, and of DILI cases, 90% were in PLHIV (35). Other risk factors for DILI-related hospitalizations include being female, a greater pill burden (especially with the use of rifampicin or efavirenz) and having more co-morbidities (35,36). These perspectives from various public sector hospitals give us insight into risk factors but were unable to estimate the incidence of DILI-related hospitalizations without an accurate denominator population.

South Africa has a high burden of both HIV and TB (37). Universal ART was adopted in South Africa in September 2016. AfA is a disease management program that comprises a large cohort of PLHIV who are managed according to guidelines like the WHO guidelines for lower-middle income countries (38). Use of this database provided a unique opportunity to study hospital admissions amongst PLHIV that result from liver injury, as AfA have accurately captured the International Classification of Diseases, Tenth Revision (ICD10) codes linked to patients claim data (38).

In this study, we aimed to investigate the incidence of liver injury in a large South African private sector managed care cohort of PLHIV on ART. Additionally, we aimed to explore, the severity of liver injury by estimating the incidence of liver injury-related hospital admissions, and the risk associated with specific ART drugs, anti-TB treatment, and other potential risk factors as identified in literature.

2. Methods

We conducted a retrospective study using routine clinical data from Aid for AIDS (AfA), a private sector HIV disease management program in Southern Africa. We included adult PLHIV (18 years and older) who started ART in the AfA program between 1 August 2011 and 5 September 2018. Our sample was based on an existing dataset at the time. Demographic data such as age and sex are collected by AfA when PLHIV enrol in the program. Clinical data such as ART prescriptions, CD4 count, and viral load results are captured through interaction with the disease management programme itself. Further laboratory results and hospitalization data are shared with AfA by health insurers in the interest of better patient care. PLHIV claim for treatment or hospitalization costs from their health insurers.

We divided antiretroviral exposure into efavirenz-based, nevirapine-based, PI-based ART regimens (usually comprising 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus the drug of interest) or “other”. The “other” group included PLHIV using a triple NRTI regimen, or if the third drug in their regimen was an integrase inhibitor, CCR5 receptor antagonist, or non- nucleoside reverse transcriptase inhibitors (NNRTIs) other than nevirapine or efavirenz. We excluded PLHIV who were flagged as being on ART but who had no ART records in the database.

We defined liver injury as an alanine aminotransferase (ALT) ≥120 IU/L. The subset of individuals with ALT≥200 IU/L were defined as having severe liver injury. The term “liver injury” does not imply a causal relationship with antiretrovirals or other drugs.

We defined liver injury-related hospitalizations as hospital admissions that occurred 3 days before or within 1 week of developing and elevated ALT (as defined by both ALT ≥120 IU/L and ALT ≥200 IU/L), with an ICD10 code that suggested liver injury (Supplementary Table 4). We excluded hospital admissions with ICD10 codes that indicated other non-drug-related causes of hepatitis (for example infectious, chronic, alcoholic, or autoimmune diseases).

We identified PLHIV as receiving anti-TB drugs if they claimed for rifampicin-containing anti-TB treatment or INH-prophylaxis (Supplementary Table 5), as these have the highest risk for liver injury, or had a documented TB-related hospital admission (Supplementary Table 6) (13). We assumed that their TB treatment or prophylaxis period was up until 6 months from their first medicine claim for anti-TB medications or their first TB-related hospital admission (whichever came first).

Patients were categorized as having alcohol-induced pathology if they had one or more ICD10 codes for alcohol-related admissions at any point during their follow up time (Supplementary Table 7). Unfortunately, we were unable to describe alcohol use in general as the database does not record this information.

We cleaned and analyzed the anonymized data from the AfA database using Stata SE version 15.0. We summarized age, CD4 count and viral load at ART initiation using medians and interquartile ranges (IQRs). Laboratory values were those closest to, and within 6 months before to two weeks after, ART initiation. We summarized categorical variables as frequencies (%). We used Kaplan Meier estimates to describe incidence of, and Cox regression to assess associations with, first liver injury episode (ALT $\geq$ 120 IU/L and ALT $\geq$ 200 IU/L), as well as first hospital admission associated with liver injury (ALT $\geq$ 120 IU/L and ALT $\geq$ 200 IU/L). Outcomes were expressed as incidences per 100 person years. We presented all hazard ratios with 95% confidence intervals, and p-values were considered significant at $p<0.05$. PLHIV were right censored if they died, stopped or switched their initial ART regimen, transferred out the cohort, or at database closure (5 September 2018).

Those who stopped or switched their ART regimen were censored 7 days after the stop/switch date. This was to account for any PLHIV who experienced signs and symptoms of liver injury which may have caused the termination of their original regimen.

The following variables identified from the literature were included *a priori* in the multivariable model: age, sex, CD4 count, viral load – all at ART initiation, along with antiretroviral regimen, exposure to alcohol, and anti-TB drug exposure (15,16,21,23,24,26,29,39–50). Anti-TB drug exposure was treated as a time-varying variable in the analysis. We excluded PLHIV with missing ART regimens, CD4 count at initiation or viral load at initiation.

3. Results

Table 1. Characteristics of the 92 757 ART-naïve PLHIV from the AfA cohort at ART initiation, according to whether or not they experienced liver injury as defined by ALT ≥120 IU/L

	Liver injury *n=2 126*	**No liver injury** *n=90 631*	**Total** *n=92 757*
Age			
(years)	38.22 (33.26 – 44.74)	38.38 (32.79 – 45.30)	38.37 (32.80– 45.29)
Sex			
Male	1 329 (62.51)	38 106 (42.05)	39 435 (42.51)
Female	797 (37.49)	52 525 (57.95)	53 322 (57.49)
ART regimen			
EFV-based	1 909 (89.79)	80 255 (88.55)	82 164 (88.58)
NVP-based	90 (4.23)	3 984 (4.40)	4 074 (4.39)
PI-based	92 (4.33)	4 307 (4.75)	4 399 (4.74)
Other regimen	35 (1.65)	2 085 (2.30)	2 120 (2.29)
CD4 count			
(cells/mm^3)	328 (158 – 520)	334 (194 – 510)	334 (193 – 510)
Viral load (log10)			
(copies/mL)	1.60 (1.60 – 3.49)	1.70 (1.60 – 4.28)	1.70 (1.60 – 4.28)
Alcohol-induced pathology	103 (4.84)	1 262 (0.88)	1 365 (1.47)
Anti-tuberculosis drug exposure	110 (5.16)	3 903 (3.64)	4 013 (3.66)

Abbreviations: ART – antiretroviral therapy. EFV – efavirenz. NVP – nevirapine. PI – protease inhibitors. Age, CD4 count and viral load are all described as medians and interquartile ranges in brackets. Sex, ART regimen, alcohol-induced pathology since ART initiation, and anti-tuberculosis drug exposure at any time since ART initiation are described with frequencies (%). ART regimens comprised 2 NNRTIs plus the drug listed.

Patient characteristics

We included 94 507 PLHIV. We excluded PLHIV with missing data regarding ART regimens, CD4 count at ART initiation or viral load at ART initiation. Median age was 38 years and was similar amongst those that had liver injury as defined by ALT ≥120 IU/L, and those who did not have liver injury (see Table 1). There were more females (57.43%) than males (42.57%) overall, but more males in the group that experienced liver injury. The median CD4 and viral loads at ART initiation were similar between PLHIV who had liver injury, than those who did not have liver injury.

Included are additional tables summarizing characteristics according to the other liver injury outcomes: Supplementary Table 1. ALT ≥200 IU/L, Supplementary Table 2. Hospitalizations associated with ALT ≥120 IU/L, and Supplementary Table 3. Hospitalizations associated with ALT ≥200 IU/L. There were no marked differences in patient characteristics at ART initiation when comparing PLHIV with and without all the above mentioned outcomes, except for sex. Males comprised the highest proportion of those with liver injury (Table 1 and Supplementary Table 1). However, females comprised a higher proportion of those with liver injury associated hospitalizations. (Supplementary Table 2 and Supplementary Table 3).

Table 2. Incidence per 100 person-years of liver injury defined as ALT ≥120 IU/L, ALT ≥200 IU/L, and hospitalizations due to liver injury with ALT ≥120 IU/L and ALT ≥200 IU/L, according to antiretroviral regimen in PLHIV initiating ART

	EFV-based regimen ***n=82 164***	**NVP-based regimen** ***n=4 074***	**PI-based regimen** ***n=4 399***	**Other regimen** ***n=2 120***	**Total** ***n=92 757***
ALT ≥120 IU/L	0.93 (0.89-0.98)	1.20 (0.98-1.47)	0.75 (0.61-0.92)	0.89 (0.63-1.25)	0.93 (0.89-0.97)
ALT ≥200 IU/L	0.37 (0.35-0.40)	0.61 (0.46-0.82)	0.36 (0.27-0.49)	0.50 (0.32-0.78)	0.38 (0.36-0.41)
Hospital admissions with an ALT ≥120 IU/L	0.06 (0.05-0.07)	0.11 (0.05-0.21)	0.07 (0.03-0.14)	0.08 (0.03-0.24)	0.06 (0.05-0.07)
Hospital admissions with an ALT ≥200 IU/L	0.04 (0.03-0.05)	0.08 (0.04-0.18)	0.03 (0.01-0.09)	0.08 (0.03-0.24)	0.04 (0.03-0.05)

Abbreviations: ALT – alanine aminotransferase. EFV – efavirenz. NVP – nevirapine. PI – protease inhibitors. All outcomes have been described with incidence per 100 person-years (95% confidence intervals), in terms of antiretroviral regimens.

Incidence of liver injury and related hospitalizations

The incidence of ALT ≥120 IU/L was 0.93 per 100 person-years, and the incidence of hospitalization with ALT ≥120 IU/L was 0.06 per 100 person-years. Overall, those on a nevirapine-based regimen had the highest incidence of liver injury or being hospitalized due to liver injury, when compared to those on efavirenz or PI-based regimens (Table 2).

Table 3. Duration (in days) between ART initiation and sustaining a liver injury defined as ALT ≥120 IU/L, ALT ≥200 IU/L, and hospitalizations due to liver injury with ALT ≥120 IU/L and ALT ≥200 IU/L, according to antiretroviral regimen

	EFV-based regimen	NVP-based regimen	PI-based regimen	Other regimen	Total
ALT ≥120 IU/L	362 (155 – 911)	184 (58 – 529)	1 024 (304 – 1 515)	330 (65 – 934)	363 (152 – 931)
ALT ≥200 IU/L	276 (110 – 770)	174 (44 – 368)	970 (358 – 1 449)	129 (65 – 698)	283 (101 – 794)
Hospital admissions with an ALT ≥120 IU/L	225 (51 – 495)	133 (40 – 196)	1 067 (133 – 1 412)	135 (1 – 868)	214 (51 – 542)
Hospital admissions with an ALT ≥200 IU/L	216 (59 – 479)	163 (118 – 214)	1 067 (148 – 1 412)	135 (1 – 868)	214 (73 – 479)

Abbreviations: ALT – alanine aminotransferase. EFV – efavirenz. NVP – nevirapine. PI – protease inhibitors. All outcomes have been described with medians (interquartile range)

Duration between ART initiation and liver injury

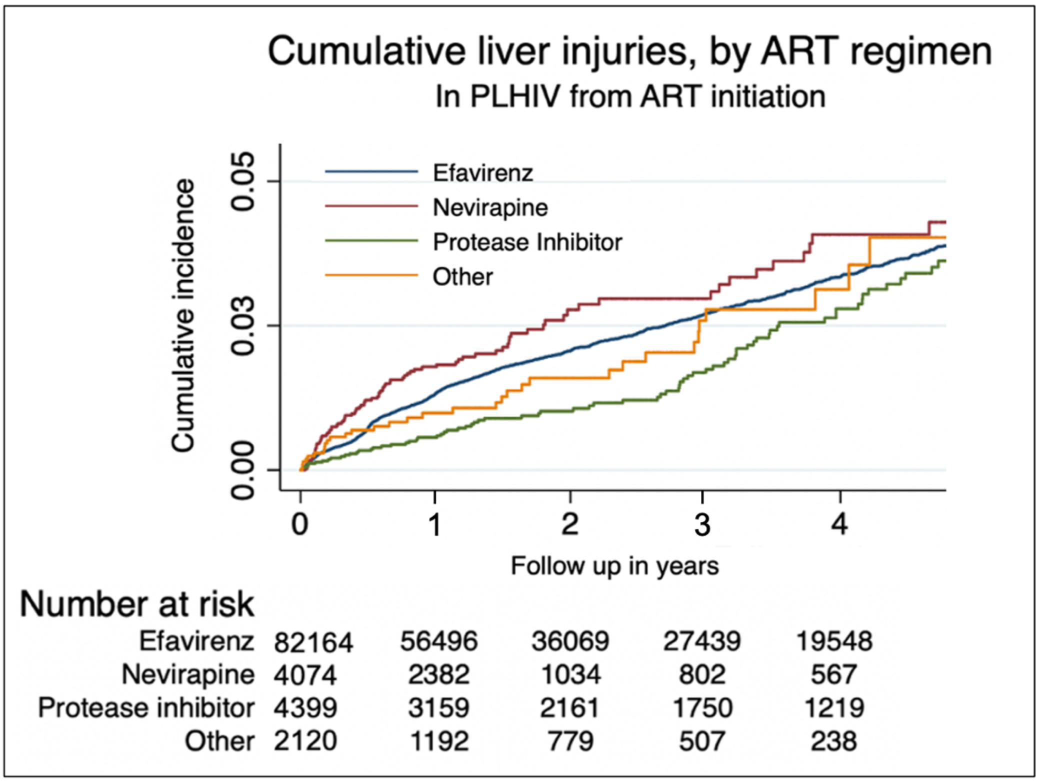
Those that experienced liver injury, experienced it at a median of 7 months to a year after ART initiation (Table 3 and Figure 1). Those on a nevirapine-based regimen experienced liver injury the soonest, at a median duration of 4-6 months after ART initiation.

Table 4. Associations between liver injury as defined by ALT ≥ 120 IU/L, and hospital admissions with a liver injury as defined by ALT ≥ 120 IU/L and risk factors.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
ALT ≥ 120 IU/L				
Age (per 10 year increase)	1.05 (0.99 – 1.10)	0.098	1.06 (1.00 – 1.12)	0.035
Male	1.13 (1.04 – 1.24)	0.006	1.12 (1.02 – 1.23)	0.017
Female	1.00 (reference)		1.00 (reference)	
NVP-based regimen	1.65 (1.34 – 2.04)	<0.001	2.74 (2.04 – 3.69)	<0.001
EFV-based regimen	1.07 (0.93 – 1.23)	0.354	1.63 (1.31 – 2.02)	<0.001
PI-based regimen	1.00 (reference)		1.00 (reference)	
Other regimen	1.17 (0.84 – 1.65)	0.353	1.96 (1.32 – 2.91)	0.001
CD4 (per 50 cells/mm^3 increase)	0.98 (0.97 – 0.99)	<0.001	0.99 (0.98 – 1.00)	0.014
logVL (per 1 log increase)	1.03 (1.00 – 1.05)	0.093	1.00 (0.97 – 1.03)	0.896
Alcohol-induced pathology	1.01 (0.83 – 1.24)	0.893	1.10 (0.90 – 1.35)	0.347
Anti-TB drug exposure	16.25 (12.97- 20.40)	<0.001	15.29 (12.14 – 19.27)	<0.001
Hospital admissions with an ALT ≥ 120 IU/L				
Age (per 10 year increase)	1.09 (0.88 – 1.35)	0.427	1.20 (0.94 – 1.52)	0.144
Male	0.96 (0.68 – 1.35)	0.827	0.94 (0.63 – 1.40)	0.746
Female	1.00 (reference)		1.00 (reference)	
NVP-based regimen	1.72 (0.84 – 3.55)	0.140	3.48 (1.24 – 9.73)	0.017
EFV-based regimen	1.08 (0.66 – 1.76)	0.766	1.50 (0.70 – 3.20)	0.299
PI-based regimen	1.00 (reference)		1.00 (reference)	
Other regimen	1.61 (0.51 – 5.09)	0.415	3.30 (0.82 – 13.26)	0.093
CD4 (per 50 cells/mm^3 increase)	0.98 (0.95 – 1.01)	0.140	0.98 (0.94 – 1.02)	0.403
logVL (per 1 log increase)	1.01 (0.92 – 1.11)	0.785	1.00 (0.87 – 1.14)	0.973
Alcohol-induced pathology	0.56 (0.26 – 1.21)	0.140	0.63 (0.28 – 1.39)	0.253
Anti-TB drug exposure	6.18 (3.16 – 12.07)	<0.001	6.27 (3.11 – 12.64)	<0.001

Abbreviations: ALT – alanine transferase. NVP – nevirapine. EFV – efavirenz. PI – protease inhibitors. ART – antiretroviral therapy. TB – tuberculosis. Reference variables – female and PI.

Figure 1. Kaplan-Meier cumulative incidence plot for time to first ALT≥120 IU/L since ART initiation



Abbreviations: ART – antiretroviral therapy. PLHIV – people living with HIV.

Predictors of liver injury

Anti-TB drug exposure had the strongest association with all liver injury outcomes, in univariate and multivariate analyses (Table 4, Supplementary Table 8). Using an efavirenz-based regimen and increasing age was significantly associated with ALT ≥120 IU/L in multivariate analyses, whereas being male and being on a nevirapine-based regimen was significantly associated in both univariate and multivariate analyses with liver injury with ALT ≥120 IU/L. As CD4 count increased, the risk for ALT≥120 IU/L decreased in both univariate and multivariate analyses. Being on a nevirapine-based regimen was associated with severe liver injury (ALT ≥200 IU/L) in both univariate and multivariate analyses, as well as for hospitalizations for liver injury with ALT≥120 IU/L in multivariate analyses. Efavirenz was significantly associated with liver injury as defined by ALT ≥200 IU/L in multivariate analyses. An increase in CD4 count was associated with decreased risk of ALT ≥200 IU/L in both univariate and multivariate analyses.

4. Discussion

This study aimed to estimate the burden and severity of liver injury in PLHIV on ART, in a large South African private sector cohort comprised of medical scheme beneficiaries. We estimated the incidence of liver injury as defined by ALT ≥120 IU/L and ALT ≥200 IU/L as 0.93 and 0.38 per 100-person years respectively. The incidence of hospitalizations due to liver injury as defined by ALT≥120 IU/L and ALT≥200 IU/L was 0.06 and 0.04 per 100 person-years respectively. The use of anti-TB drugs was strongly associated with developing liver injury and associated hospitalizations, followed by use of a nevirapine- or efavirenz-based regimen showing strong associations as well.

The incidence of liver injury in our study was significantly lower than the incidence reported in South Africa before universal ART implementation, in relatively small cohorts, where 0.26 – 17% of PLHIV on ART developed DILI as defined by ALT ≥200 IU/L (4–6). Previous studies done in Uganda and Ethiopia have also shown higher incidences of liver injury than in our study, with 4-15% of PLHIV developing grade 1-4 ALT elevations (Grade 1 (mild): 1.25-<2 x upper limit of normal (ULN), Grade 2 (moderate): 2.5 – 5.0 x ULN, Grade 3 (severe): 5.0 – 10.0 x ULN, Grade 4 (potentially life threatening): ≥ 10.0 ULN) (51–53) . Those on concurrent TB-ART therapy were 10-16 fold more likely to develop grade 1-4 ALT elevations (51,52).

Importantly, however, our study spans the first two years of universal ART implementation in South Africa. PLHIV in studies prior to 2015 generally had median CD4 counts of ≤200 cells/mm^3, where one study showed 17.6% of its cohort had CD4<50 cells/mm^3 (49,50). In contrast, PLHIV in our study had a median baseline CD4 count of 334 cells/mm^3 (95% confidence intervals: 193 – 510) which may help explain our lower incidence of liver injury. Unlike some previous studies, we found higher CD4 at ART initiation to be associated with a lower risk of liver injury. PLHIV in our study may have been on regimens that are less hepatotoxic after 2015, when compared to those prior ie efavirenz became recommended over nevirapine. Additionally we found that those on nevirapine had a shorter median time to developing liver injury compared to those on efavirenz, a similar finding in the above studies (51,52).

Previous hospital surveys have shown that, up to half of ADR-related admissions can be attributed to being on ART or anti-TB drugs (2,33–35). Our work is novel because it estimated the incidence of liver injury-related hospitalizations, in a unique cohort of PLHIV that had accurate ICD10 data available. This allowed us to better understand the burden of liver injury in the study cohort, and understand its severity through estimating the incidence of resulting hospitalizations.

We found that exposure to anti-TB drugs was the strongest predictor for developing liver injury, and being hospitalized with liver injury. This finding is not surprising given the known hepatotoxic potential of first-line anti-TB drugs (12,13). DILI can complicate TB therapy in 5-33% of all patients, affecting 9-30% of PLHIV in South Africa on ART (13). Other countries such as China, Brazil, Ethiopia and Cameroon have shown similar results (24,26,48,49,54). HIV/TB co-infection, and therefore risk of ART- and anti-TB DILI, is likely to remain a significant health burden in our setting, especially if we do not prioritize identifying and investigating safer anti-TB regimens.

As shown previously, use of nevirapine and efavirenz were also associated with an increased risk of developing liver injury. We were unfortunately unable to assess the risk of dolutegravir on developing liver injury due to limited data in our dataset. Being male was associated with an increased risk of liver injury (ALT≥120 IU/L: HR 1.13 (95% CI: 1.04-1.24) and ALT≥200 IU/L: HR 1.14 (0.99-1.30)), however sex was not statistically significantly associated with hospitalisations associated with liver injury (ALT≥120 IU/L: HR 0.96 (0.68-1.35) and ALT≥200 IU/L: HR 0.92 (0.61-1.39)). This may be due to the small event rate of hospitalisations that occur in our study, however this would need to be further evaluated in future studies.

This work has several limitations. We aimed to include PLHIV who were antiretroviral-naïve at the time of first recorded ART initiation within the AfA program. However, previous antiretroviral use may not have been recorded in the database, so it is possible that we were unable to identify accurately people who were receiving ART for the first time. We excluded those whose viral load was suppressed at the time of first documented ART initiation, as we assumed this indicated previous ART exposure. Additionally, data regarding some previously identified potential risk factors were not available in the database, namely co-infection with viral hepatitis, and treatment with cotrimoxazole; however it is estimated that <1% of the South African population has chronic HCV, and there is a 6.7% of HBV surface antigen seroprevalence in the South African population, which is rather low (55,56). We did not assess the effect of dolutegravir on liver injury, as the dataset used originated prior to formal rollout of dolutegravir in South Africa. Additionally, no data were available on alcohol use, as it was not captured in the database. We were only able to describe alcohol-induced pathology, that resulted in hospital admissions; for this reason we may have underestimated alcohol-induced pathology, as some alcohol-related pathology might not have resulted in admissions. Owing to the fact that we only used data collected via private healthcare interfaces, we may have underestimated exposure to anti-TB drugs as some TB diagnoses and/or medication prescriptions may have occurred through the public sector programs (and thus were not captured in our database). Lastly, the participants in this study were medically-insured private sector patients. These results may thus not be generalizable to the greater South African population of PLHIV due to potential differences in baseline characteristics, socioeconomic status, and other potential risk factors.

Despite these limitations, this study has bridged a gap in the literature with regards to the incidence of liver injury-related hospitalizations in PLHIV in South Africa, a setting with a high burden of HIV/TB co-infection. As a result, our study has contributed to understanding the burden of and risk factors for liver injury in our setting. Future studies could estimate the incidence and risk factors for liver injury associated with newer regimens such as dolutegravir, as well as be conducted in large cohorts in our public sector to be more generalizable to our population.

5. Conclusion

In our study, three findings are of particular note: there is a generally lower incidence of liver injury in this large cohort compared to previous studies conducted prior to universal ART implementation when nevirapine was still widely used; only a small proportion of liver injuries resulted in hospitalizations; and, finally, there is a significant association between liver injury and hospitalizations in PLHIV with anti-TB drug exposure. Our study thus demonstrates the urgent need for safer TB drugs, especially for PLHIV on ART.

6. Funding information

This research did not require any external funding sources.

7. Conflict of interest

The authors declare no conflicts of interest.

8. Ethics statement

AfA has UCT Faculty of Health Sciences (FHS) HREC's approval to collect their data (HREC REF: 858/2016, as renewed annually). This study was also approved by Human Research and Ethics Committee at the University of Cape Town FHS (Ref: 824/2019, as renewed annually). This study complies with the Declaration of Helsinki.

9. Authors' contributions

All authors contributed to and approved the final manuscript. KC conceived the initial project idea. SS, with assistance from RD and HM, analyzed the data; SS, RD, HM, and KC interpreted the data; SS drafted the manuscript; and RD, HM, and KC revised the manuscript through multiple draft adaptations. RD attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

10. Patient consent statement

AfA has HREC approval to collect anonymized routine clinical data for research purposes. PLHIV were not asked to provide consent.

11. Data availability statement

Data are accessible in principle by applying directly to AfA. Use of this data is restricted to specific approved protocols.

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Part C. Appendices

1. **Supplementary Table 1.** Characteristics of 92 757 ART-naïve PLHIV from the AfA cohort at ART initiation, according to whether or not they experienced liver injury as defined by ALT ≥200 IU/L

	Severe liver injury ***n=875***	**No severe liver injury** ***n=91 882***	**Total** ***n=92 757***
Age			
(years)	38.12 (33.02 – 44.49)	38.38 (32.80 – 45.30)	38.38 (32.80 – 45.29)
Sex			
Male	497 (56.80)	38 938 (42.38)	39 435 (42.51)
Female	378 (43.20)	52 944 (57.62)	53 322 (57.49)
ART regimen			
EFV	763 (87.20)	81 401 (88.59)	82 164 (88.58)
NVP	46 (5.26)	4 028 (4.38)	4 074 (4.39)
PI	46 (5.26)	4 353 (4.74)	4 399 (4.74)
Other regimen	20 (2.29)	2 100 (2.29)	2 120 (2.29)
CD4 count			
(cells/mm^3)	323 (151 – 508)	334 (194 – 510)	334 (193– 510)
Viral load (log10)			
(copies/mL)	1.60 (1.60 – 3.80)	1.70 (1.60 – 4.28)	1.70 (1.60 – 4.28)
Alcohol-induced pathology	50 (5.71)	1 315 (1.43)	1 365 (1.47)
Antituberculosis drug exposure	118 (13.49)	3 961 (4.31)	4 079 (4.40)

Abbreviations: EFV – efavirenz. NVP – nevirapine. PI – protease inhibitors. ART – antiretroviral therapy. Variables: Age, CD4 count and viral load have all been described as medians and interquartile ranges in brackets. Sex, ART regimen, alcohol use since ART initiation, and antituberculosis drug exposure since ART initiation have been described with frequencies (%).

2. **Supplementary Table 2.** Characteristics of 92 757 ART-naïve PLHIV from the AfA cohort at ART initiation, according to whether or not they experienced hospitalizations due to liver injury as defined by ALT ≥120 IU/L

	Hospitalization with liver injury ***n=145***	**Hospitalization with no liver injury** ***n=92 612***	**Total** ***n=92 757***
Age			
(years)	40.28 (35.13 – 46.81)	38.37 (32.80 – 45.29)	38.37 (32.80 – 45.29)
Sex			
Male	72 (49.66)	39 363 (42.50)	39 435 (42.51)
Female	73 (50.34)	53 249 (57.50)	53 322 (57.49)
ART regimen			
EFV	125 (86.21)	82 039 (88.58)	82 164 (88.58)
NVP	8 (5.52)	4 066 (4.39)	4 074 (4.39)
PI	9 (6.21)	4 390 (4.74)	4 399 (4.74)
Other regimen	3 (2.07)	2 117 (2.29)	2 120 (2.29)
CD4 count			
(cells/mm^3)	259 (98 – 460)	334 (194 – 510)	334 (193 – 510)
Viral load (log10)			
(copies/mL)	1.70 (1.60 – 4.76)	1.70 (1.60 – 4.28)	1.70 (1.60 – 4.28)
Alcohol-induced pathology	7 (4.83)	1 358 (1.47)	1 365 (1.47)
Antituberculosis drug exposure	30 (20.69)	4 049 (4.37)	4 079 (4.40)

Abbreviations: EFV – efavirenz. NVP – nevirapine. PI – protease inhibitors. ART – antiretroviral therapy. Variables: Age, CD4 count and viral load have all been described as medians and interquartile ranges in brackets. Sex, ART regimen, alcohol use since ART initiation, and antituberculosis drug exposure since ART initiation have been described with frequencies (%).

3. **Supplementary Table 3.** Characteristics of 92 757 ART-naïve PLHIV from the AfA cohort at ART initiation, according to whether or not they experienced hospitalizations due to liver injury as defined by ALT ≥200 IU/L

	Hospitalisation with severe Liver injury ***n=101***	**Hospitalisation with no severe liver injury** ***n=92 656***	**Total** ***n=92 757***
Age			
(years)	39.73 (33.44 – 47.61)	38.37 (32.80 – 45.29)	38.37 (32.80 – 45.29)
Sex			
Male	49 (48.51)	39 386 (42.51)	39 435 (42.51)
Female	52 (51.49)	53 270 (57.49)	53 322 (57.49)
ART regimen			
EFV	87 (86.14)	82 077 (88.58)	82 164 (88.58)
NVP	6 (5.94)	4 068 (4.39)	4 074 (4.39)
PI	5 (4.95)	4 394 (4.74)	4 399 (4.74)
Other regimen	3 (2.97)	2 117 (2.28)	2 120 (2.29)
CD4 count			
(cells/mm^3)	287 (126 – 471)	334 (193 – 510)	334 (193 – 510)
Viral load (log10)			
(copies/mL)	1.68 (1.60 – 4.64)	1.70 (1.60 – 4.28)	1.70 (1.60 – 4.28)
Alcohol-induced pathology	5 (4.95)	1 360 (1.47)	1 365 (1.47)
Antituberculosis drug exposure	23 (22.77)	4 056 (4.38)	4 079 (4.40)

Abbreviations: EFV – efavirenz. NVP – nevirapine. PI – protease inhibitors. ART – antiretroviral therapy. Variables: Age, CD4 count and viral load have all been described as medians and interquartile ranges in brackets. Sex, ART regimen, alcohol use since ART initiation, and antituberculosis drug exposure since ART initiation have been described with frequencies (%).

4. **Supplementary Table 4.** ICD10 codes used to define acute liver-injury related hospital admissions (72,73)

Diagnoses and clinical signs with associated elevated ALT	**ICD10 Code**	**Frequency[1] N=1 779**
Acute and subacute hepatic failure	K72.0	87
Central haemorrhagic necrosis of liver	K76.2	0
Granulomatous hepatitis, not elsewhere (74)	K75.3	10
Hepatic failure, unspecified with/without coma	K72.90/91	241
Hepatomegaly with splenomegaly, not elsewhere classified	R16.2	38
Hepatomegaly, not elsewhere classified	R16.0	127
Hepatorenal syndrome	K76.7	7
Inflammatory liver disease, unspecified	K75.9	395
Liver disease, unspecified	K76.9	295
Liver transplant status	Z94.4	0
Nonspecific reactive hepatitis	K75.2	10
Nonspecific elevation of transaminase and lactic acid dehydrogenase	R74.0	0
Other specified diseases of liver	K76.8	110
Other specified inflammatory liver diseases	K75.8	33
Toxic liver disease	K71	0
Toxic liver disease with acute hepatitis	K71.2	57
Toxic liver disease with cholestasis	K71.0	12
Toxic liver disease with fibrosis and cirrhosis of liver	K71.7	0
Toxic liver disease with hepatic necrosis	K71.1	39
Toxic liver disease with hepatitis, not elsewhere classified	K71.6	47
Toxic liver disease with other disorders of liver	K71.8	11
Toxic liver disease, unspecified	K71.9	48
Unspecified jaundice, excludes neonatal	R17	212

[1] Frequency refers to the number of ICD10 codes related to liver injury recorded in the database, not the number of PLHIV who were hospitalized with the specified ICD10 codes

5. **Supplementary Table 5.** Anti-tuberculosis drug exposure

Diagnoses	**ICD10 Code**	**Frequency**[2] **N=1 369**
Acute pancreatitis	K70.1	9
Possible alcohol related pathology	K85.9	530
Alcohol-induced chronic pancreatitis	K86.0	3
Alcoholic cardiomyopathy	I42.6	3
Alcoholic gastritis	K29.2	13
Alcoholic liver disease (including fatty liver, fibrosis, hepatitis, cirrhosis)	K70.0, K70.4, K70.9	9
Alcoholic myopathy	G72.1	0
Alcoholic polyneuropathy	G62.1	0
Degeneration of the nervous system due to alcohol eg cerebellar ataxia	G31.2	2
Hospitalisation for alcoholic rehabilitation	Z50.2	18
Mental and behavioural disorders due to alcohol use	F10.0 – F10.9	782

[2] Frequency refers to the number of ICD10 codes related to admissions with alcohol-induced pathology recorded in the database, not the number of PLHIV who were hospitalized with the specified ICD10 codes

6. **Supplementary Table 6.** Anti-tuberculosis drug exposure

Active drugs	**Frequency**[3] **N = 11 809**
Rifampicin, Isoniazid, Ethambutol, Pyrazinamide	9 909
Isoniazid	60
Rifampicin, Isoniazid	1 669
Rifampicin	171

[3] Frequency refers to the number of drug claims recorded in the database, not the number of PLHIV who received the drug

7. **Supplementary Table 7.** ICD10 codes used to define alcohol-induced pathology

Diagnoses and clinical signs with associated elevated ALT	**ICD10 Code**	**Frequency[1] N=1 779**
Acute and subacute hepatic failure	K72.0	87
Central haemorrhagic necrosis of liver	K76.2	0
Granulomatous hepatitis, not elsewhere (74)	K75.3	10
Hepatic failure, unspecified with/without coma	K72.90/91	241
Hepatomegaly with splenomegaly, not elsewhere classified	R16.2	38
Hepatomegaly, not elsewhere classified	R16.0	127
Hepatorenal syndrome	K76.7	7
Inflammatory liver disease, unspecified	K75.9	395
Liver disease, unspecified	K76.9	295
Liver transplant status	Z94.4	0
Nonspecific reactive hepatitis	K75.2	10
Nonspecific elevation of transaminase and lactic acid dehydrogenase	R74.0	0
Other specified diseases of liver	K76.8	110
Other specified inflammatory liver diseases	K75.8	33
Toxic liver disease	K71	0
Toxic liver disease with acute hepatitis	K71.2	57
Toxic liver disease with cholestasis	K71.0	12
Toxic liver disease with fibrosis and cirrhosis of liver	K71.7	0
Toxic liver disease with hepatic necrosis	K71.1	39
Toxic liver disease with hepatitis, not elsewhere classified	K71.6	47
Toxic liver disease with other disorders of liver	K71.8	11
Toxic liver disease, unspecified	K71.9	48
Unspecified jaundice, excludes neonatal	R17	212

[1] Frequency refers to the number of ICD10 codes related to liver injury recorded in the database, not the number of PLHIV who were hospitalized with the specified ICD10 codes

8. **Supplementary Table 8.** ICD10 codes used to define tuberculosis-related hospital admissions

Diagnoses	**ICD10 Code**	**Frequency**[4] **N = 21 620**
Acute miliary tuberculosis of a single specified site	A19.0	33
Acute miliary tuberculosis of multiple sites	A19.1	64
Acute miliary tuberculosis, unspecified	A19.9	122
Chylous effusion	J94.0	8
Meningeal tuberculoma	A17.1	23
Miliary tuberculosis, unspecified	A19.9	783
Other miliary tuberculosis	A19.8	84
Other respiratory tuberculosis, confirmed bacteriologically and histologically	A15.8	206
Respiratory tuberculosis unspecified, without mention of bacteriological, molecular or histological confirmation	A16.9	298
Other tuberculosis of nervous system	A17.89	176
Tuberculous pleurisy, without mention of bacteriological or histological confirmation	A16.5	166
Primary respiratory tuberculosis, confirmed bacteriologically and histologically	A15.7	288
Respiratory tuberculosis unspecified, confirmed bacteriologically and histologically	A15.9	999
Respiratory tuberculosis unspecified, without mention of bacteriological or histological confirmation	A16.9	3 567
Tuberculosis complicating pregnancy, childbirth and the puerperium	O98.0	38
Tuberculosis of adrenal glands	A18.7	11
Tuberculosis of bones and joints	A18.0	612
Tuberculosis of ear	A18.6	2
Tuberculosis of eye	A18.5	8
Tuberculosis of genitourinary system	A18.1	89
Tuberculosis of intestines, peritoneum and mesenteric glands	A18.3	1 147
Tuberculosis of intrathoracic lymph nodes, without mention of bacteriological, molecular or histological confirmation	A16.3	112
Tuberculosis of intrathoracic lymph nodes, confirmed bacteriologically and histologically	A15.4	66
Tuberculosis of larynx, trachea and bronchus, confirmed bacteriologically and histologically	A15.5	12
Tuberculosis of larynx, trachea and bronchus, without mention of bacteriological or histological confirmation	A16.4	22
Tuberculosis of lung, confirmed by sputum microscopy with or without culture	A15.0	1 591
Tuberculosis of lung, bacteriological, molecular and histological examination not done	A16.1	119
Tuberculosis of lung, bacteriologically and histologically negative	A16.0	129
Tuberculosis of lung, confirmed by culture only	A15.1	184
Tuberculosis of lung, confirmed by unspecified means	A15.3	2 076
Tuberculosis of lung, confirmed histologically	A15.2	582

Tuberculosis of lung, without mention of bacteriological, molecular or histological confirmation	A16.2	5 314
Tuberculosis of nervous system	A17+	2
Tuberculosis of nervous system, unspecified	A17.9+	70
Tuberculosis of other organs	A18	3
Tuberculosis of other specified organs	A18.8	359
Tuberculosis of skin and subcutaneous tissue	A18.4	32
Tuberculous disorders of intestines, peritoneum and mesenteric glands	K93.0*	478
Tuberculous meningitis	A17.0+	968
Tuberculous peripheral lymphadenopathy	A18.2	517
Tuberculous pleurisy, confirmed bacteriologically and histologically	A15.6	70
Tuberculous pleurisy, without mention of bacteriological or histological confirmation	A16.5	194

[4] Frequency refers to the number of ICD10 codes related to tuberculosis-related hospitalisations recorded in the database, not the number of PLHIV who were hospitalized with the specified ICD10 codes

9. **Supplementary Table 9.** Univariate and multivariate Cox proportional regression analysis to show the risk factors for developing liver injury as defined by ALT ≥ 200 IU/L, and hospital admissions with a liver injury as defined by ALT ≥ 200 IU/L . HR = hazard ratio.

Variable	**Univariate analysis**		**Multivariate analysis**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
ALT ≥200 IU/L				
Age (per 10yr increase)	0.98 (0.91 – 1.07)	0.686	1.00 (0.92 – 1.09)	0.973
Male	1.14 (0.99 – 1.30)	0.065	1.12 (0.97 – 1.29)	0.127
Female	1.00 (reference)		1.00 (reference)	
NVP-based regimen	1.72 (1.27 – 2.32)	<0.001	3.01 (1.97 – 4.61)	<0.001
EFV-based regimen	1.10 (0.90 – 1.35)	0.336	1.74 (1.28 – 2.37)	<0.001
PI-based regimen	1.00 (reference)		1.00 (reference)	
Other regimen	1.29 (0.82 – 2.04)	0.268	2.39 (1.38 – 4.13)	0.002
CD4 (per 50 cells/mm^3 increase)	0.97 (0.96 – 0.99)	<0.001	0.98 (0.97 – 1.00)	0.047
logVL (per 1 log increase)	1.07 (1.02 – 1.12)	0.003	1.02 (0.97 – 1.07)	0.469
Alcohol use	0.96 (0.72 – 1.29)	0.799	1.07 (0.79 – 1.44)	0.668
Antituberculosis drug exposure	13.55 (10.09 – 18.20)	<0.001	12.63 (9.31 – 17.12)	<0.001
Hospital admissions with an ALT ≥ 200 IU/L				
Age (per 10yr increase)	1.15 (0.90 – 1.46)	0.262	1.24 (0.94 – 1.63)	0.121
Male	0.92 (0.61 – 1.39)	0.704	0.95 (0.57 – 1.57)	0.840
Female	1.00 (reference)		1.00 (reference)	
NVP-based regimen	1.31 (0.57 – 3.01)	0.528	3.56 (0.93 – 13.65)	0.064
EFV-based regimen	1.22 (0.68 – 2.21)	0.505	1.97 (0.69 – 5.58)	0.204
PI-based regimen	1.00 (reference)		1.00 (reference)	
Other regimen	1.58 (0.50 – 5.03)	0.437	4.47 (0.95 – 21.07)	0.059
CD4 (per 50 cells/mm^3 increase)	0.96 (0.93 – 1.00)	0.065	0.97 (0.92 – 1.02)	0.243
logVL (per 1 log increase)	1.02 (0.91 - 1.15)	0.696	0.99 (0.84 – 1.17)	0.937
Alcohol use	0.77 (0.31 – 1.90)	0.568	0.82 (0.32 – 2.10)	0.674
Antituberculosis drug exposure	6.12 (2.90 – 12.91)	<0.001	5.68 (2.58 – 12.48)	<0.001

Abbreviations: ALT – alanine transferase. NVP – nevirapine. EFV – efavirenz. PI – protease inhibitors. ART – antiretroviral therapy. Reference variables – female and PI.

A. Letter of Approval from Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50-Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 January 2020

HREC REF: 824/2019

Dr R de Waal
CIDER, Level 5
School of Public Health & Family Medicine
Falmouth Building

Dear Dr de Waal

PROJECT TITLE: INCIDENCE OF, AND RISK FACTORS FOR, LIVER INJURY IN PATIENTS INITIATING ANTIRETROVIRAL THERAPY IN A PRIVATE SECTOR OBSERVATIONAL COHORT. (MASTER'S DEGREE - MS SUNITA SINHA)

Thank you for your response, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to approval from AfA to access their database being submitted.

Approval is granted for one year until the 30 January 2021

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Ms Sunita Sinha will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 824/2019

Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

B. Letter of Renewal from Human Research Ethics Committee – approved till 30th December 2022

HUMAN RESEARCH ETHICS COMMITTEE
03 DEC 2021
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.12.22
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Signed by candidate	Date Signed	6/12/21

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
Thank you for the deviation document

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	26 November 2021		
HREC REF Number	824/2019	Current Ethics Approval was granted until	30/01/21
Protocol title	Incidence of, and risk factors for, liver injury in patients initiating antiretroviral therapy in a private sector observational cohort.		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes	✓ No	
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr Renee de Waal		
Department / Office Internal Mail Address	Renee.dewaal@uct.ac.za		

5 July 2021 Page 1 of 7 FHS016

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

C. Letter of Approval from Human Research Ethics Committee – approval till 30th December 2024

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) **This serves as notification of annual approval, including any documentation described below.**			
☑ Approved	Annual progress report	Approved until/next renewal date	30/12/2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	17/1/2023

HUMAN RESEARCH ETHICS COMMITTEE
17 JAN 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	23 November 2022			
HREC REF Number	824/2019	Current Ethics Approval was granted until		30/12/22
Protocol title	Incidence of, and risk factors for, liver injury in patients initiating antiretroviral therapy in a private sector observational cohort.			
Protocol number (if applicable)				
Are there any sub-studies linked to this study?		☐ Yes	✓ No	
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.				
Principal Investigator	Dr Renee de Waal			

28 February 2022 Page 1 of 7 FHS016

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

D. Letter of Approval from Human Research Ethics Committee for AfA data collection (renewed annually)

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

HUMAN RESEARCH ETHICS COMMITTEE
16 JAN 2020
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.2021
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	11/1/2020

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	13 Jan 2020		
HREC REF Number	858/2016	Current Ethics Approval was granted until	30 Jan 2020
Protocol title	Aid for AIDS and Medscheme cohort joining cohort collaboration: IeDEA-SA sub-study linked to R007/2015 (Grant Number U01AI069924, PIs (Egger and Davies))		
Principal Investigator	Gary Maartens		
Department / Office Internal Mail Address	Division of Clinical Pharmacology, K45 Old GSH Building		
1.1 Does this protocol receive US Federal funding?		✓ Yes	☐ No

2. Protocol status (tick ✓)

✓	Research-related activities are ongoing
☐	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		
Total number of records or specimens collected, reviewed or stored since last progress report		
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	✓ Yes Attached	☐ No

4. Signature

Signature of PI		Date	13 Jan 2020

23 July 2014 Page 1 of 1 FHS017
(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)

E. Instructions for Authors from Pharmacoepidemiology and Drug Safety

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Author Guidelines updated 13th October 2021

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