A Decade of Hepatitis C at the UCT/GSH Liver Clinic in the Pre-DAA era

ROZEENA NORDIEN

NRDROZ001

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Supervisors: Prof Mark Sonderup, Prof Wendy Spearman

Department of Medicine and Division of Hepatology

University of Cape Town/Groote Schuur Hospital

University of Cape Town

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TABLE OF CONTENTS

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Rozeena Nordien

Date: 23 July 2018

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LIST OF TABLES

ABBREVIATIONS

AFP	alpha fetoprotein
ARV	antiretroviral
ASN	asunaprevir
BOC	boceprevir
COT	completion of treatment
DAA	direct-acting antiviral
DCV	daclatasvir
DSV	dasabuvir
EBR	elbasvir
ELISA	Enzyme-Linked Immunoassay
EVR	early virological response: defined as an undetectable HCV-RNA or > 2 log reduction of HCV-RNA at 12 weeks of treatment.
FDA	Food and Drug Association
FBC	Full blood count
GM-CSF	Granulocyte-Colony Stimulating Factor
GSH	Groote Schuur Hospital
GT	genotype
GZR	grazoprevir
Hb	haemoglobin
HBV	hepatitis B virus
HBcIgG	hepatitis B core IgG antibody
HBcIgM	hepatitis B core IgM antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCVcAb	hepatitis C virus core antibody

HCVcAg	hepatitis C virus core antigen
HCW	healthcare worker
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IFN-lambda-3	interferon-lambda-3
IL28B	interleukin 28B
IFN	standard interferon
IFN-α	interferon-alfa
IQR	interquartile range
INR	international normalised ratio
LDV	ledipasvir
MCC	Medicines Control Council
MSM	men who have sex with men
MTCT	mother-to-child transmission
NANBH	non-A non-B hepatitis
NAT	nucleic acid testing
OBV	ombitasvir
PCR	polymerase chain reaction
Peg-IFN	Pegylated interferon
Peg-IFN/RBV	Pegylated interferon and ribavirin
PI	protease inhibitor
PLWHA	people living with HIV/AIDS
POC	point-of-care
PTV	paritaprevir
PWID	people who inject drugs
PWUD	people who use drugs
RCT	randomised controlled trial
RBV	Ribavirin
RNA	ribonucleic acid

RTV	ritonavir
RVR	rapid virological response: defined as an undetectable HCV-RNA at 4 weeks of treatment.
SMV	simeprevir
SOF	sofosbuvir
SA	South Africa
SAHPRA	South African Health Products Regulatory Authority
SVR	sustained virological response: defined as an undetectable HCV-RNA 24 weeks after the end of treatment
SVR 12	sustained virological response at 12 weeks of treatment
SVR 24	sustained virological response at 24 weeks of treatment
SVR 48	sustained virological response at 48 weeks of treatment
TVR	telaprevir
UCT	University of Cape Town
VEL	velpatasvir
WHO	World Health Organisation

ABSTRACT

Background

Hepatitis C (HCV) in South Africa is incompletely characterised and understood. Epidemiological and clinical data will better inform our understanding and assist national policy decision making. On the background of more than two decades of clinical challenges in HCV management, the advent of direct acting antivirals (DAA) now makes HCV elimination plausible. To better understand the base from which we come, we elected to review and characterise our HCV experience at Groote Schuur Hospital (GSH) in the Pegylated interferon (Peg-IFN) and Ribavirin (RBV) management era.

Methods

Patients with chronic HCV attending GSH Liver Clinic from 2002 to 2014, were included, in the analysis. Relevant data were extracted from a registry and existing clinical records accessed. Two brands of Peg-IFN were available and those treated with the first generation add-on protease inhibitor, telaprevir, were included.

Results

238 patients were included in the analysis, median age of 47 (IQR 37-58) years, men 60.5%. Men were significantly younger than women, 43.5 (35-52) vs 55 (42-64) years, respectively, $p<0.0001$. Ethnically, the majority were white (55.9%) or mixed-ancestry (21.8%), 16.4% were HIV co-infected, 3.7% hepatitis B (HBV) co-infected and 0.4% triple infected with HCV, HBV and HIV. The most likely mode of HCV acquisition was blood/blood product exposure prior to 1992 (32.8%) and injecting drug use (IDU) 17.6%, while 30.3%, had no clear risk factor identifiable. Genotypes (GT) 1 to 5 were observed with GT-1 (34.9%) predominating. In those biopsied, (n=90), 30% ≥F3 fibrosis, with 15.6% cirrhotic. With IL28B polymorphisms, heterozygous CT (23.9%) and CC genotype (15.5%), were most frequent. 32.6% accessed Peg-IFN/Ribavirin-based therapy, 6.5% (n=5) with add-on telaprevir. GT-1 (35.1%) was most prevalent in the treatment group, followed by GT-3 (26%) and GT-5 (18.2%); 10% were HIV co-infected. Overall SVR rate was 75.3% with 37% of GT-1 not achieving SVR; 49.4% experienced adverse events

including cytopaenias (32.5%) and depression (15.6%) with 15.6% requiring erythropoietin for anaemia and 15.6% GM-CSF for neutropaenia.

Conclusion

HCV patients in the Peg-IFN/Ribavirin management era typified the epidemiology of HCV. GT distribution was pangenotypic and treatment outcomes were encouraging despite treatment challenges. Patient selection, IL28B and sensible cytopaenia support, likely accounted for this. However numbers treated were limited and the DAA era of therapy allows for a rapid expansion of therapy with now growing numbers of patients and a changing local epidemiology.

CHAPTER 1: LITERATURE REVIEW

INTRODUCTION

In 2016 at the 69th World Health Assembly, the World Health Organisation's (WHO) first Global Health Sector Strategy to eliminate viral hepatitis was approved and adopted by member states. The aim of the strategy is to eliminate viral hepatitis by 2030 being defined as a 65% reduction in mortality from end-stage liver disease and a 90% reduction in the incidence of new infections. (1) Up to 2014, the standard of care for the management of hepatitis C virus (HCV) for more than a decade, prior to the advent of the direct-acting antiviral (DAA) era of therapy, was Pegylated interferon and Ribavirin (Peg-IFN/RBV). The response to therapy was variable and dependent on a number of viral and host factors. In addition to a variable response, adverse events and intolerability of therapy was significant. Overall, approximately 50% of patients responded to therapy with a sustained virological response (SVR), defined then as being hepatitis C polymerase chain reaction (PCR) negative 24 weeks after the end of treatment (EOT) and were cured. Since the advent of the DAAs, all oral therapies are possible and in excess of 90% of patients can be cured, making the goal of elimination achievable provided that HCV-infected individuals are identified and appropriately linked to care.

The global HCV prevalence is approximately 1% and translates to an estimated 71.1 million people with active hepatitis C viraemia. HCV is a leading cause of chronic liver disease worldwide and the global burden of disease continues to increase as those infected develop the potential long-term complications of cirrhosis, hepatocellular carcinoma (HCC), liver failure and death. (2) Notably, 36.7 million people are currently living with Human Immunodeficiency Virus (HIV) infection globally. (3) HCV thus has a greater net burden than HIV (4), a fact not often appreciated given the infection is invariably silent for 2 - 3 decades before long-term complications develop. Of note, HIV co-infection significantly alters the natural history of hepatitis C resulting in accelerated fibrosis and progression to cirrhosis and an increased risk of HCC as well as reduced response to interferon-based therapy. (5-8)

EPIDEMIOLOGY OF HCV IN SUB-SAHARAN AFRICA AND SOUTH AFRICA

Sub-Saharan Africa has a significant HCV disease burden and accounts for approximately 15-20% of the burden of infections globally. Good epidemiological data is limited and reported prevalences are inconsistent. (9) A suggested seroprevalence is 3% with approximately 10.1 million individuals being viraemic, as per modelled data. (10) The region is pan-genotypic with genotypes 1 and 4 encountered most frequently. (4)

Epidemiology and prevalence in South Africa of chronic hepatitis C remains poorly characterised. The suggested prevalence rates in South Africa are often based on blood donor data which is a poor representation of the real HCV burden given that many high risk groups are excluded from being donors. Few data exists on defined cohorts of patients with chronic HCV in South Africa, as regards: genotype distribution, disease presentation and progression, access to treatment, long-term outcomes and response to treatment. The prevalence of HCV viraemia in South Africa in 2015, is likely between 0.4 and 0.9% in the general population but is greater in high-risk groups especially people who inject drugs (PWID). It is estimated that 600 000 to 800 000 South Africans are viraemic for HCV. (2) Recent data from a large national screening study of key and vulnerable populations determined a HCV viraemic rate of 44% in people who inject drugs (PWID), 6% in people who use drugs (PWUD), and 2% in men who have sex with men (MSM). There was marked geographical and regional variability with the highest rates in Pretoria and similar, albeit lower, rates in Cape Town, Johannesburg, Durban and Port Elizabeth. Genotypes 1a and 3a predominated with a handful of genotype 4 observed. HIV co-infection was frequent at 12.2% in PWID. (11)

HEPATITIS C VIROLOGICAL CHARACTERISTICS

Hepatitis C was first observed and described by Feinstone et al. in 1975, and identified as the commonest cause of transfusion-associated hepatitis. It was named non-A, non-B hepatitis (NANBH) given that hepatitis A and hepatitis B were the only identified hepatitis viruses at the time. (12) In 1989, in a laboratory at Cheiron, Choo and his colleagues, cloned and sequenced the genome of hepatitis C. (13, 14)

HCV is a single-stranded positive-sense ribonucleic acid (RNA) virus belonging to the flaviridae family and replicates almost exclusively in hepatocytes. The viral RNA polymerase lacks a “proofreading” ability which results in the simultaneous presence of different viral variants, defined as quasi-species in the same host. The genome undergoes constant mutation and often escapes human immunological detection and elimination leading to chronic infection. (15, 16) Through phylogenetic analysis, the genetic heterogeneity was categorised into 7 major genotypes and 67 subtypes. (17)
Genotypes 1 and 3 are the most prevalent globally, and account for 46% and 30% of infection, respectively. Genotypes 2, 4 and 6 comprise 9%, 8% and 6% of all infections, respectively and genotype 5 has a 1% prevalence. Genotype 7 has only been observed in a few individuals in Central Africa. (18) The distribution of genotypes in Sub-Saharan Africa varies and is essentially a pan-genotypic region with genotypes 1 and 4 predominating. (19) In South Africa, the most prevalent genotype in blood donors is genotype 1 (34%). However, in the overall population, the commonest are genotypes 5a and 1 with a prevalence of 35% and 31%, respectively and genotypes 2, 3 and 4 comprising 2%, 14% and 14%, respectively with 4% having mixed genotypes. (9) This high degree of genetic heterogeneity determines treatment regimens and creates a major challenge for the development of HCV vaccines. (17)

ROUTES OF TRANSMISSION AND HIGH RISK GROUPS

HCV is most efficiently transmitted through parenteral inoculation. Prior to the implementation of routine screening of blood donor products in the early 1990’s, blood or blood product transfusions posed a major risk factor for the transmission of HCV infection in developed countries. This risk was substantially reduced following the implementation of blood product screening, (20) which was introduced in South Africa in 1992. Unfortunately, some low and middle income countries still have inconsistent or sub-standard testing, usually due to financial implications of screening. (21) Other routes of transmission of HCV include injecting drug use, tissue and organ transplants, unsafe medical procedures or injection practices, health care worker (HCW) parenteral exposure (eg. needle-stick injuries), traditional scarification, body piercings, sexual transmission

(MSM mainly) and mother-to-child transmission (MTCT) especially in HIV/HCV co-infected pregnant women. (22)

SCREENING FOR HCV

There is limited data as regards the cost-effectiveness of HCV screening approaches in low and middle income countries. Review of the available literature suggests that testing of high-risk groups such as prisoners, PWID, MSM and HIV-infected individuals is likely cost-effective. Outside the setting of populations known to have a high HCV prevalence, routine screening has not been proven to be cost-effective. (23) With minimal data available as to prevalence rates and modes of transmission in South Africa, planning cost-effective screening programmes is challenging. A recent review describes the prevalence and risk factors among South African MSM who inject drugs. (24) Here, the suggested seroprevalence was 27%. Other at risk populations in South Africa such as people living with HIV/AIDS (PLWHA), transgender individuals, sex workers and prisoners, must be included in future screening programmes. (24) Awareness campaigns encouraging routine testing in high-risk groups needs to be instituted as well as giving PWID access to syringe and needle exchange programmes as well as assisting with opiate addiction via opiate drug-substitution therapy. (25) De-stigmatisation plays a key role in addressing this considerable burden of disease globally. (24)

The Western Province Blood Transfusion Service (WPBTS) which services the Western Cape and the South African National Blood Service (SANBS) which services the rest of South Africa perform the only formal HCV screening in South Africa. These blood donor services practice judicious blood and blood product screening, including pan nucleic acid tests, which has virtually eliminated transfusion-associated viral hepatitis and HIV. Donors who are screened and found to be HIV, HCV or HBV infected are appropriately informed and referred for further evaluation and management. The implementation of screening programmes outside the blood transfusion service, does not exist. There is urgent need for the implementation of routine screening in the appropriate populations as well as linkage to care and treatment, appropriate follow up and ultimately cure.

In order to make routine screening for HCV more accessible and cost-effective, the WHO prequalified its first point-of-care (POC) rapid diagnostic tests in 2016/2017. The SD BIOLINE HCV test and the OraQuick HCV Rapid Antibody Test both have sensitivities and specificities approaching 100% when compared to laboratory-based testing. (26) Where laboratories are accessible, screening is best performed using immunoassays such as an enzyme-linked immunosorbent assay (ELISA). If this is positive, a confirmation is required using HCV-RNA nucleic acid testing (NAT) to establish whether there is active viraemia. (4) Quantitative NAT has been used to measure HCV viral load and monitor treatment response. Qualitative testing allows for rapid and sensitive detection of virus below a defined threshold. HCV core (p22) antigen (HCVcAg) is an alternative to detect active viraemia as well as being used to monitor treatment response and confirm SVR. (27)

CLINICAL MANIFESTATIONS AND NATURAL HISTORY OF DISEASE

Hepatitis C has acute and chronic clinical manifestations and the course of the infection varies among individuals. The acute infection is often asymptomatic and thus goes undetected in the majority of infected individuals. The long asymptomatic course makes it important to establish routine screening in high-risk populations.

Clinical manifestations can present about 8 weeks following exposure and symptoms include anorexia, fatigue, jaundice and malaise. HCV rarely causes fulminant hepatic failure. (15) Acute HCV infection is characterised by the appearance of HCV RNA, HCV core antigen, and subsequently HCV antibodies within six months of infection with HCV. It is estimated that approximately 20 - 30% of HCV infected patients will undergo spontaneous viral clearance. Certain factors which reduce the likelihood of spontaneous clearance include injection drug use, HIV co-infection, excessive alcohol consumption, black race, non-genotype 1 infection and asymptomatic presentations. (28) The IL28B polymorphism and DQB1*0301 allele of the histocompatibility complex class II, are two genetic host factors with a strong association with spontaneous viral clearance. (29)

Chronic HCV infection occurs in 45 - 84% of infected individuals after acute exposure with chronicity defined as the persistence of HCV RNA within blood for more than six months. Chronic HCV infection is a slowly progressive disease with chronic hepatic necro-inflammation resulting in cirrhosis in approximately 20% of patients over two to three decades of infection. Once cirrhosis is established, HCC develops in 1 - 4% of these individuals per year and the annual risk of developing decompensated liver failure is 3 - 6% per year. (29, 30)

Chronic HCV infection is also associated with extra-hepatic manifestations. These include sicca syndrome, porphyria cutanea tarda, lichen planus, type 2 diabetes, and non-Hodgkin's lymphoma. Between 15% and 30% of individuals will have circulating cryoglobulins and 5-25% of these individuals will develop essential cryoglobulinaemia, systemic vasculitis, peripheral neuropathy, Raynaud's phenomenon, and membranoproliferative glomerulonephritis. (31)

Progression to fibrosis is variable and there are numerous co-factors which increase an individual's risk. These factors include HIV or HBV co-infection, acquiring infection at an older age, male gender, excess alcohol consumption, insulin resistance, type 2 diabetes mellitus, immunosuppressive therapy, and host genetic factors. (29) Achieving an SVR is defined as having no viral RNA present 24 weeks after completing Peg-IFN/RBV therapy or 12 weeks after completing DAA therapy. SVR reduces complications associated with chronic liver disease as well as the extra-hepatic complications, thereby improving quality of life and reducing morbidity and mortality. (29)

With Peg-IFN/RBV therapy, liver biopsy was essential to assess both the degree of necro-inflammation (histological grade) and the presence and stage of liver fibrosis as well as other negative co-factors such as steatohepatitis and iron overload as this determined both the indication for therapy as well as the likelihood of an SVR. In the DAA era, staging liver disease remains important, because it influences treatment duration and whether RBV is required as add-on therapy, but this is usually assessed non-invasively with the Fibroscan®. Prior to non-invasive methods such as Fibroscan®, histological evaluation of the liver biopsy remained the gold standard for determining the activity of HCV-related

liver disease and assessing fibrosis, thereby predicting prognosis and likelihood of progression of disease. Histologically HCV infection consists of lymphocyte infiltration in the parenchyma, lymphoid follicles in portal areas, and reactive bile duct changes. (32) Biopsy can also be useful in excluding other causes of liver disease (autoimmune hepatitis, alcoholic liver disease, drug-related liver injury, iron overload and steatohepatitis).

Different histological scoring systems for hepatitis C infection are available including the Batts-Ludwig, METAVIR and Ishak systems. The METAVIR system – the most widely used – incorporates both a grading and staging system. The grading system assesses necro-inflammation. The staging system assesses the degree of fibrosis. The grades range from 0-4 with 0 being no activity, 1 mild activity, 2 moderate activity and 3 or 4 varying severe activity. In the staging system (0-4), stage F1 denotes minimal fibrosis, F2 scarring that extends outside the areas that contain blood vessels, F3 bridging fibrosis and F4 denotes cirrhosis. (33)

THE HEPATITIS C TREATMENT ERAS

INTERFERON-BASED THERAPIES

In the early 1990's, the potential benefits of interferon-alfa therapy (IFN-α) for HCV infection, was documented. Two randomised controlled trials (RCTs) using a 24-week course of treatment with IFN-α demonstrated that this therapy improved serum alanine aminotransferase (ALT) levels and liver histology. These effects were dose-dependent with greater improvements noted with three times weekly injections of 2 to 3MU (46-48%) of IFN as opposed to 1MU (28%) three times a week or control (0-8%) groups. Efficacy was measured at the end of therapy, while still on IFN and demonstrated that HCV RNA was eradicated in some patients. (34, 35) Following these outcomes the United States Food and Drug Administration (FDA) approved IFN-α2b for the management of chronic HCV in 1991. (36) Despite viral eradication with IFN therapy, the one trial demonstrated that 80% of responders had relapsed one year after completion of treatment (COT). (34) The cure rate (defined as an SVR 6 months after COT) for IFN monotherapy was between

15 and 20%. A few years later Ribavirin (RBV), an oral antiviral agent with an undefined but probable immunomodulatory action, was added to IFN therapy. The combination was found to be superior to IFN alone in terms of virological, biochemical and histological end points. RCTs demonstrated that SVR rates of approximately 30-40% were achieved. (37, 38) Dose reduction or treatment cessation was more often required in patients receiving combined IFN/RBV therapy. The most frequent reason for discontinuation of therapy in groups receiving IFN-monotherapy or combined IFN/RBV, was psychiatric adverse events and notably depression. Depression resulted in the cessation of treatment in 2-9% of patients. (37) The RBV metabolite accumulates in red blood cells and results in a reversible haemolytic anaemia. It was observed that 36% of subjects developed anaemia, up to 20% will have a haemoglobin (Hb) level drop below 10g/dl and 8.5g/dl in 5%. (39) 50% of subjects experience influenza-like symptoms, 25% have psychiatric symptoms of which 20% are severe including acute psychosis, severe depression and personality change. Fatigue or myalgia is experienced in 20% of patients, and gastritis or gastroenteritits in 10%. (37)

Pegylated interferon (Peg-IFN) was developed to enhance the half-life of IFN. There are two types of Peg-IFN, namely Peg-IFN-alfa-2a and Peg-IFN-alfa-2b which are equally as efficient. (40) From 2000 with the advent of once weekly dosed Peg-IFN, standard of care for the management of HCV, for almost two decades, became Peg-IFN and RBV (Peg-IFN/RBV). The response to therapy was genotype and host factor dependent with significant adverse side effects and overall less than a 50% chance of a cure. SVR rates of 70-80% for HCV genotype 2 or 3 infections and 45-70% for other genotypes were documented. (41) Genotype 1 achieved much lower SVR rates of approximately 40%. (42, 43) In a randomised trial, over 3000 patients with chronic HCV genotype 1 infection were assigned to receive 48 weeks of treatment with either Peg-IFN-alfa-2b at standard dose (1.5 µg per kilogram of body weight per week) or a low dose (1.0 µg per kilogram per week), plus RBV at a dose of 800 to 1400 mg per day, or Peg-IFN-alfa-2a at a dose of 180 µg per week plus RBV at a dose of 1000 to 1200 mg per day. (40) The safety and adverse-event profiles and efficacy data were similar among subjects treated with low-dose or standard-dose Peg-IFN-alfa-2b or Peg-IFN-alfa-2a, combined with varying RBV dosages. Despite improved cure rates, these regimens were associated with significant

adverse effects requiring dose reduction and/or cessation of therapy. The most common adverse effects among all three groups included influenza-like symptoms, depression and haematological side-effects including anaemia and neutropaenia. Between 12.5% and 21.1% of subjects required dose reduction and 2.1-5.9% required discontinuation of therapy, because of neutropaenia. 23.2-28.2 % of subjects met the Hb criteria for RBV-dose reduction (between 8.5 and 10g/dl) and between 2.1 and 3.8% required discontinuation of therapy, because of an Hb <8.5g/dl. Psychiatric symptoms were mild to moderate and resulted in treatment cessation in 1.8-2.6% of subjects.(40)

In 2009, Dongliang Ge et al. reported that a genetic polymorphism near the *IL28B* gene on chromosome 19, encoding interferon-lambda-3 (IFN-lambda-3) was found to be associated with an approximately twofold greater rate of SVR in response to treatment, both among patients of European ancestry and African-Americans. Only individuals with genotype 1 were included in this study. The IL28B polymorphism is associated with both natural clearance of the virus as well as treatment response. (44) When genotyped at the IL28B polymorphism site into IL28B CC, CT or TT; the IL28B CC genotype was associated with a more favourable treatment response when compared to non-CC genotypes. (45) The presence of IL28B CC was used to decide on the suitability of a HCV-infected individual for Peg-IFN/RBV therapy as this polymorphism improved the SVR. Since the advent of the DAAs, pan-genotypic therapies are possible and SVR is obtainable in more than 90% of cases irrespective of IL28B polymorphisms.

SOUTH AFRICAN HEPATITIS C MANAGEMENT GUIDELINES 2005 AND 2010

The risk-benefit of treatment was an important consideration when making therapeutic decisions. Factors such as quality of life, age, co-morbidities, virological factors and histological assessment all influenced decision to treat. Patients at increased risk of developing cirrhosis required treatment.

Indications for treatment (2005)

1. Moderate or severe chronic hepatitis infection as characterised by stage F2 or F3 fibrosis (METAVIR scoring system) regardless of the necro-inflammatory grade and patients with A2 and A3 disase (METAVIR scoring system).

2. Mild chronic hepatitis (F0 or F1) or chronic hepatitis associated with normal transaminases. The long-term benefits of treatment in the absence of excessive alcohol consumption, HCV/HIV co-infection and obesity was not yet established. Liver transaminases fluctuate and these patients should be monitored every 4-6 months.
3. Patients with compensated cirrhosis were considered for treatment on an individual basis in order to stabilise disease and prevent complications such as HCC.
4. Relapsers or non-responders after IFN-monotherapy or IFN/RBV combination therapy. Relapse is defined as detectable HCV-RNA in serum within 6 months following the end of treatment (EOT). Non-response is defined as detectable HCV-RNA at the completion of treatment (COT).
5. Treatment was contraindicated in patients with liver transplants.
6. Treatment with IFN-monotherapy was strongly recommended in patients with acute HCV infection. Long-term effects of Peg/IFN had not yet been established in this group.
7. Special populations:

a. Patients with alcohol dependence needed a period of abstinence from alcohol for at least 1 year prior to the initiation of treatment.
b. Patients using recreational drugs required a multidisciplinary approach including rehabilitation programmes, psychological and psychiatric assessment.
c. Treatment can worsen psychiatric disorders and patients with pre-existing psychiatric disease needed to be clinically stable prior to being treated.

   The decision to treat patients with HIV/HCV co-infection depended on liver biopsy results and the immune status of the patient. Patients with a CD4 count > 200, warranted treatment for the HCV first. In patients established on antiretroviral therapy (ARV), the indications to treat were based on the same histological criteria as those without HIV.

8. Patients with HCV/HBV co-infection: a liver biopsy, HCV and HBV viral load and genotype were important in deciding on appropriate management.
9. Other intercurrent disorders:

a. Haematological:

i. Liver biopsy was contraindicated in haemophiliacs and there was no need to change treatment regimens.
ii. Thalassaemic patients: RBV was contraindicated.

b. Renal impairment:

i. RBV and IFN are contraindicated in non-dialysed patients.
ii. IFN is relatively contraindicated following renal transplant.

In 2010, the following changes were made with regards to indications for treatment:

1. The METAVIR activity score was no longer used as a criteria for therapy.
2. Symptomatic cryoglobulinaemia was included as an indication to treat.

<u>The following contraindications were also included in the 2010 guidelines:</u>

1. Under 2 years of age
2. Untreated thyroid disease
3. Autoimmune conditions (including autoimmune hepatitis), known to be exacerbated by Peg-IFN and RBV
4. Decompensated liver disease
5. Severe concurrent medical conditions including coronary artery disease, cardiac dysfunction, hypertension, chronic obstructive airways disease or poorly controlled diabetes mellitus
6. Pregnancy or patients unwilling to use adequate contraception
7. Severe depressive illness which is not yet established on medication
8. Hypersensitivity to medication used to treat HCV
9. Solid organ transplantation

Liver Biopsy

Except where contraindicated, all patients being considered for treatment required a liver biopsy. The pre-treatment liver biopsy assisted in identifying other pre-existing liver conditions as well as grading fibrosis and necro-inflammatory activity.

Treatment

Drugs approved for treatment of chronic HCV included: interferon alfa-2a, interferon alfa-2b, interferon alfacon-I, peginterferon alfa-2a, peginterferon alfa-2b and Ribavirin.

Peg/RBV combinations:

1. Peg-IFN-alfa-2a 180µg weekly subcutaneously (s/c) + Ribavirin (800-1200mg/day)
2. Peg-IFN-alfa-2b (1-1.5 µg/kg/week) s/c + Ribavirin (800-1200mg/day)

Treatment duration:

Genotype 1 and 4: 48 weeks of treatment.

Genotype 2 and 3: 24 weeks of treatment.

Genotype 5 and 6: 48 weeks of treatment.

The 2010 guidelines included the following:

Patients with genotype 1 or 4 with a delayed response (HCV RNA negative between 12 and 24 weeks), were considered for an extended course of therapy for 72 weeks. Patients who received treatment through 48 to 72 weeks and have a negative HCV RNA, were retested 24 weeks after the EOT, to establish whether they have obtained an SVR. Due to a data lack, genotypes 5 and 6 were treated as genotype 1, for a duration of 48 weeks. Patients with genotype 2 or 3 with a delayed response (HCV RNA negative between 12 and 24 weeks), were considered for an extended course of therapy for 48 weeks. These patients who had a negative HCV RNA at the EOT, had repeat testing performed 24 weeks later to establish whether they had obtained an SVR.

Treatment indications

- Previously untreated patients without contraindications for therapy.
- Patients with HIV/HCV co-infection who have received no prior therapy for HCV. HCV therapy should follow the initiation of ARV and close attention needs to be paid to drug-drug interactions.
- Relapsers after IFN-monotherapy.
- Non-responders to IFN-monotherapy.

Peg-IFN monotherapy was indicated in patients where RBV was contraindicated.

Standard IFN monotherapy was indicated in patients with acute HCV infection or patients on dialysis. Liver transplantation was indicated in patients with decompensated cirrhosis.

Supportive measures

Serious adverse effects such as neutropaenia, anaemia and thrombocytopaenia, required dose-adjustment or discontinuation of treatment.

1. Neutropaenia could be managed with Granulocyte-Colony Stimulating Factor (GM-CSF).

2. Anaemia could be managed by concomitant administration of erythropoietin and maintaining the patient on 80% of the dose.

Obesity

Obesity is a risk factor for steatosis and increases the progression of fibrosis. HCV also aggravates insulin resistance. Patients with a BMI>25kg/m^2, are encouraged to lose weight prior to the initiation of therapy.

Vaccination

Patients who are not immunised, should receive vaccination against HAV and HBV.

Venesection

Venesection is recommended in patients who have iron overload present on liver biopsy.

Evaluation prior to initiating treatment

A full physical examination including the eyes and urinalysis is mandatory prior to initiating treatment.

Baseline blood tests required include:

Haematology: Full blood count (FBC), INR and PTT.

Chemistry: Electrolytes, urea, creatinine, liver function tests, uric acid, cholesterol, alpha-fetoprotein (AFP)

Thyroid function tests: TSH and FT4.

HCV-RNA, genotype and viral load.

HIV ELISA

HBsAg, anti-HBs, HBcore IgG

A pregnancy test was to be done 1 day prior to starting treatment in all female patients and in all female partners of male patients who are of childbearing age.

Emotional status needed evaluation as depression was not uncommon and suicides were reported.

Monitoring during treatment

Haematology and chemistry: At weeks 1, 2, 4, 6 and 8 and then every 4 weeks.

TSH, FT4: Every 12 weeks.

Pregnancy test: Every 4 weeks.

Two effective modes of contraception (barrier method + other) must be used for the entire duration of therapy.

Patients receiving Peg-IFN/RBV had a quantitative HCV-RNA test at 12 weeks. Individuals who had a detectable HCV-RNA > 50 IU/mL (i.e have not obtained early virological response) or a drop in viral load <2 $\log^{10}$, are unlikely to achieve SVR and treatment may be stopped. Patients with cirrhosis potentially benefited from continued treatment and the decision to stop depended on the assessment by the physician on an individual basis.

Investigations 8 weeks after COT:

Haematology: FBC

Chemistry: ALT

Investigations 24 weeks after COT:

Haematology: FBC

Chemistry: ALT

HCV-RNA (qualitative). Failure to detect HCV-RNA at this point is considered SVR or cure.

DIRECT-ACTING ANTIVIRAL THERAPIES

Table 1 lists the different directly acting antivirals and their sites of action.

DAAs directly inhibit viral replication by targeting essential viral proteins. Four main classes have been developed which inhibit three viral proteins: NS3/4A protease inhibitors, NS5A inhibitors and two types of NS5B polymerase inhibitors. The 'first-wave' of DAAs was approved in 2011 for the treatment of HCV genotype 1 infection. The first protease inhibitors were the NS3/4A inhibitors, Telaprevir (TVR) and Boceprevir (BOC) that were administered in combination with Peg-IFN/RBV as triple therapy. SVR rates improved from 40% with interferon-based regimens, to 70-80% using the triple therapy with BOC or TVR and shortened treatment duration. (46-48). Adverse effects were still

considerable and often resulted in therapy intolerability and treatment cessation. In 2013, a second generation protease inhibitor, Simeprevir was approved and achieved SVR rates between 75 and 86% in genotype 1 infected patients with slightly higher rates in patients treated with higher doses and longer duration of therapy. (49) Antiviral activity was also demonstrated in all other HCV genotypes, except genotype 3. (50)

In the same year, an NS5B polymerase inhibitor, Sofosbuvir (SOF) was administered as triple therapy alongside PegIFN/RBV. It has pan-genotypic antiviral activity, is well tolerated and genotype 2 and genotype 4 patients achieved high rates of SVR. While rates of SVR in genotype 3 were lower, outcomes were improved with longer duration of treatment. (51)

Interferon-free therapies that combine two or more DAAs have improved tolerability and efficacy. Two or more DAA classes are used with or without RBV in order to increase the barrier to resistance. Phase 3 trials of daclatasvir (DCV) plus asunaprevir (ASN), ombitasvir (OBV) plus paritaprevir (PTV)/RBV and sofosbuvir plus ledipasvir (LDV) have shown fewer side-effects and improved SVR rates. (52) ASN plus DCV was the first interferon-free DAA therapy achieving SVR rates of 78% when used alone and 95% when used in combination with PegIFN/RBV, to treat patients with genotype 1 infection. (53)

DCV plus ASN therapy (54) and SOF plus LDV, (55) have been approved for treatment of genotype 1 infection, and SOF plus RBV has been approved for genotype 2 infection. (56)

The combination of SOF and LDV is recommended for genotype 1 and genotype 4-6 infection, with phase 3 trials showing SVR rates between 94% and 99% in genotype 1 patients. (57)

PTV/ritonavir (RTV), OBV, and dasabuvir (DSV), with or without RBV is an alternative to SOF/LDV and ASN/DCV therapies. (52) A second generation protease inhibitor grazoprevir (GZR) demonstrates pan-genotypic antiviral activity. Treatment-naïve

genotype 1 patients were treated with a combination of GZR and elbasvir (EBR) and achieved a 93% SVR rate. (58)

A RBV-free combination of SOF and Simeprevir (SMV) has been shown to be effective in treating genotype 1 and genotype 4 infection. SVR rates of 97% were achieved in patients with genotype 1 infection without cirrhosis and 83% in patients with cirrhosis. (59)

The combination of SOF and DCV with or without RBV is effective in genotype 1, 2 and 3 achieving SVR rate of 98%, 92% and 89%, respectively. (60)

In 2016, the FDA approved the first fixed-dose combination pan-genotypic regimen. The RBV-free SOF and velpatasvir (VEL) has been shown to be an effective pan-genotypic therapy. In a phase 3 trial, patients achieved SVR rates of 98%, 100%, 100%, 97%, and 100% for genotype 1, 2, 4, 5 and 6, respectively. (61)

Glecaprevir and Pibrentasvir is a fixed-dose combination regimen of a new generation NS3/4A inhibitor and NS5A inhibitor with potent pan-genotypic antiviral activity. This combination has a high barrier to resistance and in 3 phase 3 studies produced SVR rates of 93% in patients without cirrhosis infected with genotype 2, 4, 5 and 6. (62) In another phase 3 trial, the combination of glecaprevir and pibrentasvir resulted in high rates of SVR among patients without cirrhosis who had genotype 1 infection (>99%) and genotype 3 infection (95%). A treatment duration of 8 weeks yielded non-inferior SVR rates when compared to 12 weeks of therapy. (63)

CONCLUSION

In order to achieve the WHO goal of viral hepatitis elimination by 2030, there is a need for accurate global epidemiological data, identification of HCV-infected individuals and linkage to care. The lack of data with regards to defined cohorts in South Africa needs to be addressed. This study documented our local experience with regards to the burden of disease, patient demographics and treatment outcomes with Interferon-based therapy.

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Table 1. Direct acting antivirals and sites of action

Protease inhibitor		
NS3/4A inhibitor	**NS5A inhibitor**	**NS5B inhibitor**
Telaprevir	Daclatasvir	Sofosbuvir
Boceprevir	Ledipasvir	Dasabuvir
Simeprevir	Elbasvir	
Grazoprevir	Ombitasvir	
Paritaprevir	Velpatasvir	
Asunaprevir	Odalasvir	
Voxileprevir		
Glecaprevir		

Burstow NJ, Mohamed Z, Gomaa AI, Sonderup MW, Cook NA, Waked I, et al. Hepatitis C treatment: Where are we now? Int J Gen Med. 2017;10:39-52.

CHAPTER 2: PUBLICATION READY MANUSCRIPT

A Decade of Hepatitis C at the UCT/GSH Liver Clinic in the Pre-DAA era

R Nordien[1], MW Sonderup[1], CW Spearman[1].

1. Division of Hepatology, Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital.

Corresponding author: Mark W Sonderup (msonderup@samedical.co.za)

ABSTRACT

Background
Hepatitis C (HCV) in South Africa is incompletely characterised and understood. Epidemiological and clinical data will better inform our understanding and assist national policy decision making. On the background of more than two decades of clinical challenges in HCV management, the advent of direct-acting antivirals (DAA) now makes HCV elimination plausible. To better understand the base from which we come, we elected to review and characterise our HCV experience at Groote Schuur Hospital (GSH) in the pegylated interferon (Peg-IFN) and ribavirin (RBV) management era.

Methods
Patients with chronic HCV attending GSH Liver Clinic from 2002 to 2014, were included in the analysis. Relevant data were extracted from a registry and existing clinical records accessed. Two brands of Peg-IFN were available and those treated with the first generation add-on protease inhibitor, telaprevir, were included.

Results
238 patients were included in the analysis, median age of 47 (IQR 37-58) years, men 60.5%. Men were significantly younger than women, 43.5 (35-52) vs 55 (42-64) years, respectively, $p<0.0001$. Ethnically, the majority were white (55.9%) or mixed-ancestry (21.8%), 16.4% were HIV co-infected, 3.7% hepatitis B (HBV) co-infected and 0.4% triple infected with HCV, HBV and HIV. The most likely mode of HCV acquisition was blood or blood product exposure prior to 1992 (32.8%) and injecting drug use (IDU) 17.6%, while 30.3%, had no clear risk factor identifiable. Genotypes (GT) 1 to 5 were observed with GT-1 (34.9%) predominating. In those biopsied, (n=90), 30% ≥F3 fibrosis, with 15.6% cirrhotic. With IL28B polymorphisms, heterozygous CT (23.9%) and CC genotype (15.5%), were most frequent. 32.6% accessed Peg-IFN/Ribavirin-based therapy, 6.5% (n=5) with add-on telaprevir. GT-1 (35.1%) was most prevalent in the treatment group, followed by GT-3 (26%) and GT-5 (18.2%); 10% were HIV co-infected. Overall SVR rate was 75.3% with 37% of GT-1 not achieving SVR; 49.4% experienced adverse events including cytopenias (32.5%) and depression (15.6%). A total of 23.4% of patients required cell support in the form of erythropoietin and/or GM-CSF.

Conclusion
HCV patients in the Peg-IFN/Ribavirin management era typified the epidemiology of HCV. GT distribution was pangenotypic and treatment outcomes were encouraging despite treatment challenges. Patient selection, IL28B and sensible cytopenias support, likely accounted for this. However numbers treated were limited and the DAA era of therapy allows for a rapid expansion of therapy with now growing numbers of patients and a changing local epidemiology.

Introduction

In 2016 World Health Assembly of the World Health Organisation (WHO) approved the first Global Health Sector Strategy to eliminate viral hepatitis. The aim of the strategy is to eliminate viral hepatitis by 2030, and was defined as a 90% reduction in the incidence of new infections with a consequent 65% reduction in mortality from associated liver disease.[1] Globally, hepatitis C virus (HCV) prevalence is 1% equating to an estimated 71.1 million people with active hepatitis C viremia resulting in HCV being a leading cause of chronic liver disease. The global burden of liver disease continues to increase due to hepatitis C related cirrhosis, hepatocellular carcinoma, liver failure and death.[2] The epidemiology and prevalence of chronic HCV in South Africa (SA), remains poorly characterised and understood. Few data exists in defined cohorts of patients with chronic HCV and responses to therapy. The modelled prevalence of HCV viremia in SA, as of 2015, is between 0.4 and 0.9 %, with genotype 1b (22.1%) thought to be most frequent, although genotypes 1 to 5 are prevalent.[2]

Following the identification and sequencing of HCV in 1989 by Choo and colleagues,[3] the management of chronic HCV infection has undergone a revolution. Initially, treatment with standard interferon yielded poor response rates.[4] Consequently, pegylated interferon and oral ribavirin (Peg-IFN/RBV) enhanced response with sustained virological response (SVR) rates of ~ 50%.[5] Despite improved SVR rates, treatment was costly and associated with significant adverse effects that resulted in patients discontinuing therapy. Cytopenias associated with drug toxicities sometimes necessitated erythropoietin (EPO) and/or granulocyte macrophage colony-stimulating factor (GM-CSF) to support treatment sustainability.[5] Factors influencing a positive treatment outcome included the ability to complete >80% of the planned duration of treatment with >80% of the required doses of Peg-IFN and ribavirin,[6] the IL28B polymorphism genotype, the baseline viral load, degree of liver fibrosis and genotype. In 2012, the first of a new generation of add-on oral protease inhibitors, specifically for genotype 1 HCV, emerged. These drugs, telaprevir and boceprevir, significantly improved SVR rates but at the expense of enhanced adverse effects.[7-9] The advent of the all oral direct-acting antivirals (DAA) for hepatitis C has revolutionised therapy with SVR response rates now exceeding 95% with fewer adverse effects. The success of DAA therapy has made HCV elimination now very plausible.

The initial availability of Peg-IFN/RBV in South Africa emerged in 2002, and by 2004, the University of Cape Town/Groote Schuur Hospital (UCT/GSH) Liver Clinic was able to access this standard of care for HCV-infected individuals via several mechanisms including compassionate use or expanded access treatment programmes, a hospital allocated budget to treat a limited number of HCV-infected individuals annually or private funding. Given the advent of the DAA era of treatment, we elected to review and describe our experience with interferon-based therapy over a decade plus period from 2002 to 2014. We document our local experience with regards to the patient demographics; clinical, biochemical and genetic profile of the study population; viral characteristics, and treatment outcomes (side-effect profile and SVR rates) with interferon-based therapy during this period. No such data exists for South Africa, and reviewing our experience serves as a benchmark to compare the rapidly expanding, albeit currently limited, DAA era of HCV treatment in South Africa. This study hence serves to inform national policy decision making structures of the base from which we have functioned with respect to hepatitis C in South Africa.

Given the need for data in informing such policy, this study aims to support such policy structures in achieving South Africa's efforts for viral hepatitis elimination by 2030.

Methods

All patients with hepatitis C virus infection attending the UCT/GSH Liver Clinic from 2002 up to and including 2014, were included. All relevant patient demographic data and clinical characteristics were extracted from a patient registry, in addition to existing clinical records, and recorded in a database. In terms of treatment, 2 brands of Peg-IFN viz. Pegylated Interferon α-2b (Peg-Intron^{R}, Schering-Plough) and Pegylated Interferon α-2a (Pegasys^{R}, Hoffman-La Roche) were available in South Africa during the study period and patients using either product, were included. Standard Peg-IFN/RBV treatment guidelines based on genotype were followed. Patients treated with the addition of the first generation DAA therapy (Telaprevir) to their Peg-IFN/RBV regimen, were also included in the final analysis.

Laboratory tests

All baseline biochemistry, full blood count and INR were recorded. Human Immunodeficiency Virus (HIV) status was confirmed by ELISA testing for HIV antibody and p24 antigen and in those HIV co-infected, CD4 count (cells/mm^3) was recorded at the time of presentation. Viral serological testing (ARCHITECT I or II, Abbott Diagnostics) for hepatitis C (Hepatitis C IgG-antibody) was positive in all participants and active viremia confirmed by an in-house PCR technique amplifying the 5'NCR region of HCV. Genotype was determined using the Versant HCV Genotype v2.0 Line Probe Assay (Siemens AG) or through in-house NS5B sequencing. HCV viral loads were measured using the COBAS Ampliprep/Cobas TaqMan v2.0 (Roche Diagnostics). Serological testing for hepatitis A (Hepatitis A IgG antibody) and hepatitis B (HBsAg, HBcore IgG and core IgM-antibody) was performed.

Liver biopsy was used to assess fibrosis unless contraindicated (e.g. in hemophiliacs or coagulopathic patients). Liver biopsies were all assessed by one of two experienced liver histopathologists while clinicopathologic assessments were done concurrently with hepatologists. Hepatitis C was staged and graded using the METAVIR system.

Ethics approval

This study was approved by the University of Cape Town Human Research Ethics Committee (HREC REF: R045/2014).

Statistical analysis

Values are expressed as the median and interquartile range (IQR) for continuous variables. Clinical characteristics were summarised using standard descriptive characteristics. Where appropriate, differences between qualitative parameters were explored using the Wilcoxon Rank sum test. Statistical analysis was performed using Microsoft Excel (2013).

Results

Included in the evaluation of the total cohort was n=238 patients, the majority male, 60.5% (n=144) (see Table 1). The median age (IQR) of the cohort was 47 (37-58) years, however men were significantly younger than women, 43.5 (35-52) vs 55 (42-64) years, respectively, $p<0.0001$. Of

note, demographically and self-identified heterosexual male patients were significantly older than men who have sex with men (MSM), 49 (47-51) vs. 40.5 (34-45) years, respectively, p=0.0002. Ethnically, the majority of patients were white (55.9%), followed by mixed-ancestry (21.8%) and black Africans (13.9%). The likely mode of HCV acquisition was predominantly blood or blood product exposure prior to 1992 (32.8%), parenteral through injecting drug use (IDU) 17.6% or through parenteral or percutaneous exposure (10.9%) e.g. needle stick injuries, tattoos, etc. Hemophiliacs comprised 13.4% of patients. No clear route could be identified in almost a third (30.3%) of patients. In terms of genotype (GT) distribution (table 2), GT-1 (34.9%) predominated with GT-1a more prevalent than 1b, 62.7% vs. 36.3%, respectively. Genotypes 3, 4 and 5 were present in almost similar frequencies (18.1%, 17.2%, and 16% respectively) with GT-2 (6.7%) least frequent. Genotype was not identified in 7.1% of the cohort. Virologically, the median hepatitis C viral load was 5.6 (4.7-6.2) $\log^{10}$ IU/ml. In addition, 16.4% were HIV co-infected with a median baseline CD4 count of 395 cells/mm^3. In terms of HBsAg, 3.7% (n=8) were hepatitis B co-infected and 1 patient (0.4%) was triple infected with HIV, HBV and HCV. In those screened for hepatitis A immunity (anti-HAV IgG), 71.5% were positive.

Baseline laboratory characteristics are shown in Table 3 demonstrating that median baseline alanine transaminase (ALT) and aspartate transaminase (AST), were elevated, however 29.8% (n=71) had an ALT within the laboratory "normal" range. In Table 4, the biopsy features are listed (n=90). In terms of the METAVIR score, 30% had ≥F3 fibrosis, with 15.6% cirrhotic. Most had F2 fibrosis. Ancillary biopsy data demonstrated a high frequency of steatosis (63.3%) and iron overload present in 12.2%.

Table 5 notes all ancillary clinical or laboratory data. From 2011, all patients were screened for the IL28B allele. The heterozygous IL28B CT allele was most frequent followed by the homozygous CC or TT alleles. Homozygosity or heterozygosity for the HFE C282Y or H63D alleles are highlighted, with homozygosity infrequently observed. Diabetes mellitus was highly prevalent (17.6%). Although alcohol consumption was not accurately assessed, 16.4% of patients confirmed regular consumption.

Only 32.3% (n=77) of HCV-infected patients accessed Peg-IFN/RBV-based therapy (Table 6). Five patients received add-on first generation protease inhibitor treatment, viz.Telaprevir. These 5 patients were all GT-1, of whom 2 patients had previously failed treatment. Genotype distribution in the treatment group comprised GT-1 (35.1%), GT-2 (11.7%), GT-3 (26%), GT-4 (9.1%) and GT-5 (18.2%). Eight treated patients (10%) were HIV co-infected, and one triple infected. Most patients (71.5%) treated were ≥F2 fibrosis, with 28.6% ≥F3 and 14.3% compensated cirrhotics. Overall SVR was 75.3% with more than half (55.8%) achieving a rapid virological response (RVR) and 84.4% achieving an early virological response (EVR). Of the 19 patients not achieving an SVR, the majority (52.6%) were GT-1. All GT-2 patients achieved SVR. In patients tested for IL28B prior to treatment, 77%, 66% and 40% of the CC, CT and TT genotype, respectively, achieved a SVR. The median HCV viral load (log copies/ml) did not differ between those who did and did not achieve SVR, 5.85 (IQR 5.0-6.4), 5.8 (IQR 5.45-6.45), respectively, p=0.56.

Table 7 demonstrates the event rate of adverse effects related to Peg-IFN/RBV therapy with 49.4% of patients experiencing adverse effects. Surprisingly only a single patient discontinued therapy because of adverse effects. The need for cytopenia support was substantial with 7.8% and 7.8% of patients, respectively, requiring EPO for anaemia to maintain ribavirin dose or GM-CSF support to maintain Peg-IFN dose for treatment-related neutropenia. An equal number of patients required a combination of EPO and GM-CSF (7.8%). Psychiatric side effects, especially depression, presented in 15.6% of patients.

Discussion

There are several observations consistent with typical patterns of HCV epidemiology in our Liver Clinic cohort during the time period 2002 to 2014. Data now supports that 2 distinct epidemiological patterns of infection exist that creates a bimodal age distribution for chronic hepatitis C.[10] The first group are older and likely acquired infection through a variety of mechanisms including blood or blood product exposure pre-1992, injecting drug use (IDU) and other parenteral modes of infection. This is clearly reflected in our cohort with one-third having blood or blood product exposure prior to 1992. Less represented are recent or current injecting drug users, given their lower likelihood to have presented or be referred for therapy given the rigours of Peg-IFN/Ribavirin-based therapy. Current transmission, in younger patients, is driven predominantly by people who inject drugs (PWID) and MSM, especially if HIV-infected.[11] In our study, men were younger than women, and MSM were significantly younger than non-MSM patients. This is consistent with this pattern of HCV infection. In addition, we have previously documented high rates of HCV infection in HIV-positive MSM in Cape Town, South Africa.[12-14]

Globally genotypes 1 and 3 predominate, responsible for 44% and 25% respectively, of global HCV infection.[2] In a recent South African study of HCV characteristics in blood donors and the general population for the period 2008 to 2011, genotype 1 was observed in 34%, with genotype 5a being most prevalent (36%). GT-5a accounted for 54% of infections in black South Africans with genotype 1 seen in 43% of white South Africans. Genotypes 3 and 4 occurred at the same frequency (14% respectively) and least frequent was genotype 2.[11-16] The genotype distribution in our patient cohort was somewhat similar, except for GT-5a. This is not unexpected given the generally higher prevalence of GT-5a in the northern half of South Africa. GT-1 is invariably more prevalent in the Southern portion of the country. Similarly, GT-4 was more prevalent compared to HCV genotype distribution studies of the 1990s.[17] This likely reflects patterns of immigration into South Africa over the past 2 to 3 decades by people from GT-4 predominant parts of Africa. The GT-4 subtype variation also supports this notion. Furthermore, our study again reinforces the HCV pangenotypic status (GT 1 to 5) of South Africa, which has implications for elimination programmes based on DAA therapy in the future.

In terms of the mode of HCV acquisition, IDU and blood or blood product exposure dominated. This is unsurprising, however in a considerable proportion of patients, no clear mode was identifiable. Factors such as traditional or unsafe medical practices likely account for these patients' hepatitis C. This creates substantial difficulty when making recommendations on population screening for hepatitis C in South Africa as part of a national elimination strategy.

The median ALT, as anticipated, was elevated however the cohort demonstrates the well recognised phenomenon of a laboratory "normal" ALT value in a substantial component, 29.8%, of participants. This is well recognised in patients with chronic hepatitis C where typically one-quarter of patients can have so-called normal transaminases.[18] This again underpins the reason as to why ALT should not be used and is a poor surrogate marker for active hepatitis C viremia.

In the time period under review, only a third of patients accessed Peg-IFN/Ribavirin-based therapy. This is not unexpected given several reasons including the limited funding available to treat patients, the significant cost of Peg-IFN/Ribavirin treatment, the adverse effects of treatment and contraindications to treatment. In addition, patients with difficult to treat HCV genotypes or HIV co-infection with minimal fibrosis, were warehoused in anticipation of more effective therapies with fewer side effects. Despite this, the number of patients treated was substantial and represents

the single largest reported cohort of patients treated with Peg-IFN/RBV-based hepatitis C therapy in South Africa to date. Given that almost two-thirds of patients treated were the more difficult genotype 1, 4 or 5 (35.1% GT-1 alone), almost one-third with advanced fibrosis and 10% HIV co-infected, treatment outcomes in terms of SVR at 75.3% of patients, were very good. Given that SVR rates in most large cohort studies ranged between 54% and 66%, our outcomes were particularly encouraging and several reasons likely accounted for this. Firstly, patient selection is important in terms of those more motivated for treatment, more favourable IL28B genotypes and the judicious use of supportive therapy to allow for maximum dose of Peg-IFN and ribavirin to be used. In terms of patient selection, those with liver biopsies demonstrating more necro-inflammatory activity and greater degrees of fibrosis, were more likely to be offered therapy.

Looking at the IL28B single nucleotide polymorphism, of those tested, most patients had the more favourable IL28B CC or CT genotype as opposed to the less favourable TT genotype. Data from the large IDEAL study, was the first to demonstrate the significant predictive value of the relevant IL28B genotype in increasing the odds ratio in favour of a SVR. The IL28B CC genotype resulted in an odds ratio that increased the likelihood of SVR 3 to 7 times in those with the CC polymorphism genotype.[19] In keeping with this, in our study 77% and 66%, respectively of the CC and CT genotype patients, achieved an SVR as compared to 40% of the TT genotype participants.

Treatment outcomes are influenced by on treatment factors such as achieving an RVR and the ability to maintain maximum doses of Peg-IFN and ribavirin. Given the cytopenic side effects of Peg-IFN/RBV, the use of GM-CSF to maintain absolute neutrophil counts and EPO to maintain haemoglobin levels, is crucial to allow for continued regular administration of Peg-IFN/RBV at recommended doses.[5] In our treated patients, almost a quarter of patients (23.4%) received GM-CSF and/or EPO support to allow for continued dosing of Peg-IFN/RBV, respectively. This enabled patients to complete the required duration of therapy while tolerating maximal doses and likely contributed to the SVR rates achieved in our cohort. Maintaining Peg-IFN and ribavirin dosing at ≥80% has a positive effect on SVR likelihood[6]

Adverse events, as anticipated, were frequent. Rates of psychiatric adverse events, typically depression, were reported to occur in 5 – 20%.[20, 21] Just over 15% of our patients were diagnosed with depression that required an intervention either with an antidepressant and/or counselling and support. The rates of adverse events in our treated patient cohort support the difficulties of Peg-IFN/RBV-based therapy. Adverse effects tend to occur within first 12 weeks so whilst duration is affected, need for support was no different between the 2 groups viz. 24/48 weeks. We were fortunate in that only 1 patient discontinued therapy because of adverse events. Adverse effects were compounded in those patients using the add-on protease inhibitor therapy, telaprevir. Whilst numbers were small, 80% of GT-1 patients using telaprevir in conjunction with Peg-IFN/RBV, achieved SVR.

With regards to study limitations, this is a retrospective study and not all required data was available. IL28B genotyping only became available in 2011. Resource constraints resulted in a limited number of patients being treated and very careful selection was required to ensure that those treated had the greatest likelihood of cure. This selection bias may have inflated SVR rates. There may be underrepresentation of certain high risk populations such as IDU, because of them being less likely to present or be referred.

Conclusion

The HCV patient population in the Peg-IFN/RBV era in the clinic represented the more typical epidemiology of HCV acquisition either via previous IDU or blood transfusion prior to 1992. Notably we are pangenotypic in GT distribution and our treatment outcomes during this era were commendable despite significant treatment challenges and adverse events. Careful patient selection, favourable IL28B alleles and sensible cytopenia support as well as on-treatment responses with high rates of RVR and EVR, likely account for this. Our study is the first of its kind documenting outcomes with Interferon-based therapy for hepatitis C in South Africa. It will serve as a benchmark for comparison with the performance of DAAs in South Africa. Given the need for data in informing national policy decision making structures and the fact that no such data exists, this study serves to inform and support such policy structures, and encourage government to provide the economic infrastructure required to support South Africa's effort for viral hepatitis elimination by 2030, of which DAA therapy for hepatitis C, will be the foundation of management.

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Table 1. Demographic characteristics of the study population.

Parameter	N=238	P-value
Male, *n* (%)	144 (60.5)	
Heterosexual*	112 (47.1)	
MSM*	32 (13.4)	
Age† distribution, median (IQR)		
Total cohort	47 (37-58)	
Male: female	43.5 (35-52) : 55 (42-64)	0.0001
Heterosexual: MSM	49 (47-51) : 40.5 (34-45)	0.0002
Ethnicity‡, *n* (%)		
Asian	20 (8.4)	
Black	33 (13.9)	
Mixed ancestry	52 (21.8)	
White	133 (55.9)	
Mode of acquisition, *n* (%)		
Transfusions§	78 (32.8)	
Unknown	72 (30.3)	
Injection drug use	42 (17.6)	
Parenteral/percutaneous	26 (10.9)	
Unsafe medical procedures⁋	13 (5.5)	
Sexual encounter	5 (2.1)	
Perinatal Mother to Child	2 (0.8)	
Hemophiliac, *n* (%)		
Total	32 (13.4)	

The data is expressed as medians and interquartile ranges (IQR) or numbers and percentages
Abbreviations: MSM = men who have sex with men
* Sexual orientation is self-reported
† Age (years) at presentation
‡ Ethnicity is self-reported
§ Blood and blood products, including hemophiliacs
⁋ Surgical/dental/orthodontic procedures

Table 2. Viral and baseline laboratory characteristics

	N = 238	
HCV viral load (log^{10}IU/ml, median, IQR)	5.6 (4.7 - 6.2)	
Genotype, *n* (%)		
GT-1	83 (34.9)	
GT-2	16 (6.7)	
GT-3	43 (18.1)	
GT-4	41 (17.2)	
GT-5	38 (16.0)	
Not tested	17 (7.1)	
Genotype Subtype	N = 238	*n**, (%)
GT-1a	42 (17.6)	42 (62.7)
GT-1b	25 (10.5)	25 (37.3)
GT-2a	4 (1.7)	4 (50)
GT-2b	4 (1.7)	4 (50)
GT-3a	36 (15.1)	36 (97.3)
GT-3b	1 (0.4)	1 (2.7)
GT-4a	2 (0.8)	2 (22.2)
GT-4c	2 (0.8)	2 (22.2)
GT-4e	5 (2.1)	5 (55.6)
GT-5a	30 (12.6)	30 (100)
Not tested	17 (7.1)	
Serological markers		
Hepatitis A Virus		
Anti-HAV IgG† (n=123)	88 (71.5)	
Hepatitis B Virus		
HBsAg‡ (n=219)	8 (3.7)	
HIV§ (n=189)	31 (16.4)	
Baseline CD4 count (cells/mm^3)	395 (272 – 650)	
HIV/HBV/HCV⁋	1 (0.4)	

The data is expressed as medians and interquartile ranges (IQR) or numbers and percentages
GT = genotype; n = no. of patients tested.
**n* = the total no. of individuals with a genotype subtype.
% = percentage of the total no. of individuals subtyped within the genotype: GT-1 (N=67), GT-2 (N=8), GT-3 (N=37), GT-4 (N=9) and GT-5 (N=30)
†Hepatitis A IgG antibodies (hepatitis A immunity)
‡Hepatitis B surface antigen (HBV co-infection)
§HIV = Human Immunodeficiency Virus
⁋HIV/HBV/HCV = triple infected

Table 3. Baseline laboratory characteristics of the study population (N=238)

Parameter	Ref range*	Median (IQR)
TBil(μmol/L)	0 - 21	10 (7 – 16)
Alb (g/L)	35 - 52	43 (38-47)
ALT (U/L)	5 - 40	60 (35-109)
AST (U/L)	5 - 40	50 (32-89)
INR		1 (0.9-1.1)
Hb (g/dL)	13.0 - 17.0	14.4 (13.1-15.8)
WCC ($x10^9$/L)	4.0 - 10.0	6.2 (5-7.8)
Platelets (x 10^9/L)	137 - 373	225 (156-278)
AFP (μg/L)	0.0 - 7.0	3.9 (2.4 - 6.8)
Ferritin (μg/L)	30 - 400	189 (90-438)

Abbreviations: TBil = Total bilirubin; Alb = Albumin; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; INR = International normalised ratio; Hb = Haemoglobin; WCC = White cell count; Plts = Platelets; AFP = Alpha fetoprotein
*Laboratory reference range

Table 4. Liver biopsy results

No. of biopsies performed, *n* (%)	N = 238 90 (37.8)
	N = 90
Presence of steatosis, *n* (%)	57 (63.3)
Presence of iron	11 (12.2)
Metavir activity score*	
0	3 (3)
1	48 (53)
2	25 (28)
3	14 (16)
4	0 (0)
Metavir fibrosis score†	
0	9 (10)
1	15 (16.7)
2	39 (43.3)
3	13 (14.4)
4	14 (15.6)

The data is expressed as numbers and percentages
*Metavir activity score: 0=no active inflammation; 1=minimal inflammation; 2=moderate inflammation; 3=severe; 4=very severe.
†Metavir fibrosis score: 0=no fibrosis; 1=minimal fibrosis; 2=scarring fibrosis; 3=bridging fibrosis; 4=cirrhosis.

Table 5. Ancillary clinical and laboratory data, N=238

Diabetes Mellitus, *n* (%)	42 (17.6%)
HBA1C (%), median (IQR)	7.7 (6.8 – 8.8)
Hereditary Hemochromatosis (HFE genes), *n* (%)	
C282Y heterozygous	5 (2.1)
C282Y homozygous	1 (0.4)
H63D heterozygous	19 (8.0)
H63D homozygous	1 (0.4)
Not tested	147 (61.8)
Alcohol consumption*, *n* (%)	
Yes	39 (16.4)
No	199 (83.6)
IL28B Allele, *n* (%)	
CC	37 (15.5)
CT	57 (23.9)
TT	18 (7.6)
Not tested	126 (52.9)

The data is expressed as medians and interquartile ranges or numbers and percentages.
*Self-reported

Table 6. PEG-IFN/RBV treated patients

Genotype distribution	GT-1	GT-2	GT-3	GT-4	GT-5
Total treated, *n* (%) (N=77)	27 (35.1)	9 (11.7)	20 (26)	7 (9.1)	14 (18.2)
SVR*	17 (63)	9 (100)	18 (90)	4 (57)	10 (71.4)
No SVR*	10 (37)	0	2 (10)	3 (43)	4 (28.6)
Liver biopsy results (N=49)					
Metavir activity score, *n* (%)					
0	1 (2)				
1	31 (63.3)				
2	11 (22.5)				
3	6 (12.2)				
4	0 (0)				
Metavir fibrosis score, *n* (%)					
0	5 (10.2)				
1	9 (18.4)				
2	21 (42.9)				
3	7 (14.3)				
4	7 (14.3)				
SVR†	58 (75.3)				
RVR‡	43 (55.8)				
EVR§	65 (84.4)				
Treatment duration					
24 weeks	38 (49.4)				
48 weeks	37 (48.1)				
72 weeks	4 (5.2)				

Abbreviations: GT = genotype

*N = no. of patients treated in a specific GT subtype.

†SVR = Sustained virological response is defined as an undetectable HCV-RNA 24 weeks after the end of treatment.

‡RVR = Rapid virological response is defined as an undetectable HCV-RNA at 4 weeks of treatment.

§EVR = Early virological response is defined as an undetectable HCV-RNA or > 2 log reduction of HCV-RNA at 12 weeks of treatment.

Table 7. Treatment adverse effects (N=77)

Patients who experienced adverse effects	38 (49.4)
Patients stopping therapy because of adverse effects	1 (1.3)
Side-effects experienced	
Neutropenia	10 (11.7)
Anaemia	4 (5.2)
Thrombocytopenia	4 (5.2)
Bicytopenia	3 (3.9)
Pancytopenia	4 (5.2)
Psychiatric	7 (9.1)
Psychiatric and cytopenia	5 (6.5)
Rash	1 (2.6)
Cell Support Required (N=18)	
No. of patients requiring EPO	6 (7.8%)
No. of patients requiring GM-CSF	6 (7.8%)
No. of patients requiring EPO and GM-CSF	6 (7.8%)

EPO = erythropoietin; GM-CSF = Growth-Colony Stimulating Factor

CHAPTER 3: APPENDICES

APPENDIX 1: South African Medical Journal - Instructions to Authors

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study. Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.

- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:
Rather:
Each row of data must have its own proper row:
Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

APPENDIX 2: Data Capture Sheets

Date of Birth	YYYY - MM - DD
Folder number	
Age at diagnosis	

VARIABLE	KEY	DESCRIPTION
Ethnicity	1	Asian
	2	Black
	3	Coloured
	4	White
Gender	1	Female
	2	Male
Mode of transmission	0	Unknown
	1	Transfusion of blood products
	2	Intravenous drug use
	3	Parenteral or percutaneous
	4	Sexual encounter
	5	Dental/orthodontic/surgical procedure
	6	Mother-to-child transmission
IL28-B (allele)	0	Not tested
	1	CC
	2	CT
	3	TT
Sexual orientation	0	Unknown
	1	Heterosexual
	2	MSM
HBsAg	0	Not tested
	1	Positive
	2	Negative

VARIABLE	KEY	DESCRIPTION
HBcIgG	0	Not tested
	1	Positive
	2	Negative
HBcIgMG	0	Not tested
	1	Positive
	2	Negative
Hep A IgG	0	Not tested
	1	Positive
	2	Negative
HCV genotype	1	Genotype 1
	2	Genotype 2
	3	Genotype 3
	4	Genotype 4
	5	Genotype 5
	6	Genotype 6
Genotype subtype	1	a
	2	b
	3	c
	4	d
	5	e

VARIABLE	KEY	DESCRIPTION	VALUE
HCV VL IU/ml	0	Not tested	
		Numerical value	
HCV log VL	0	Not tested	
		Numerical value	
HIV	0	Not tested	
	1	Positive	
	2	Negative	
CD4	0	Not tested	
		CD4 count	

Blood Results	Numerical values	Blood Results	Numerical values	Blood Results	Numerical values	Blood Results	Numerical values
TBr		GGT		WCC		Tf sats%	
CBr		ALT		Plts		Ferritin	
TPr		AST		AFP		HBA1C (%)	
Alb		INR		Fe			
ALP		Hb		Tf			

VARIABLE	KEY	DESCRIPTION
Diabetes mellitus	1	Yes
	2	No
Raised BMI >30	0	Unknown
	1	Yes
	2	No
ETOH	1	Yes
	2	No
ALD	1	Yes
	2	No
NAFLD	1	Yes
	2	No
Haemophilia	0	Not a haemophiliac
	1	Haemophilia A
	2	Haemophilia B
HFE genes	0	Not tested
	1	Negative
	2.1	C282Y homozygous
	2.2	C282Y heterozygous
	3.1	H63D homozygous
	3.2	H63D heterozygous
Porphyria plasma scan	0	Not tested
	1	Positive
	2	Negative
Liver biopsy	1	Yes
	2	No
Metavir activity score	0	No active inflammation
	1	Minimal inflammation
	2	Moderate
	3	Severe inflammation
	4	Very severe inflammation
	5	Not applicable
Metavir fibrosis score	0	No fibrosis
	1	Minimal fibrosis
	2	Scarring
	3	Bridging fibrosis
	4	Cirrhosis
	5	Not applicable
Steatosis	0	Not applicable
	1	Yes
	2	No
Iron	0	Not applicable
	1	Yes
	2	No
Treated or Not Treated	1	Yes
	2	No

VARIABLE	KEY	DESCRIPTION
Treatment duration	1	24 weeks
	2	48 weeks
	3	72 weeks
	4	Other
PCR 4	0	Not applicable
	1	Positive
	2	Negative
PCR12	0	Not applicable
	1	Positive
	2	Negative
PCR24	0	Not applicable
	1	Positive
	2	Negative
PCR48	0	Not applicable
	1	Positive
	2	Negative
PCR72	0	Not applicable
	1	Positive
	2	Negative
SVR	0	Not applicable
	1	Yes
	2	No
Treatment side-effects	0	Not applicable
	1	Yes
	2	No
Side effects experienced	0	Not applicable
	1	Neutropaenia
	2	Anaemia
	3	Thrombocytopaenia
	4	Bicytopaenia
	5	Pancytopaenia
	6	Psychiatric
	7	Cytopaenia and psychiatric (7)
	8	Rash (8)
G-CSF (eg. Neupogen)	0	Not applicable
	1	Yes
	2	No
EPO (eg. Recormon)	0	Not applicable
	1	Yes
	2	No
Telapravir used	0	Not applicable
	1	Yes
	2	No
Other DAA used	0	Not applicable
	1	Yes
	2	No

APPENDIX 3: Ethics Approval

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

03 April 2018

HREC REF: 206/2018

A/Prof Mark Sonderup
Hepatology
K-floor, OMB

Dear A/Prof Sonderup

PROJECT TITLE: A DECADE OF HEPATITIS C AT THE UCT/GSH LIVER CLINIC IN THE PRE-DAA ERA (MMED CANDIDATE - DR R NORDIEN) SUB-STUDY LINKED TO R045/2014

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 April 2019.

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)

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.

The HREC acknowledge that the student, Dr Rozeena Nordien will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
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 Convention on Harmonisation 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.