NELISWA ANTONIA GOGELA

STUDENT NO: GGLNEL001

SUPERVISOR: A/PROF MW. SONDERUP

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TITLE: HEPATITIS C PREVALENCE IN HIV INFECTED HETEROSEXUAL MEN AND MEN WHO HAVE SEX WITH MEN

Declaration

I, **Neliswa Antonia Gogela**, 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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Signature: Signed by candidate

Date: 20th September 2018……

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Chapter 1

Acknowledgements and contributions

Acknowledgements

Master Matome Mafokwane and Master Itumeleng Mafokwane: To my boys. I love you and I am really grateful to God for you and for all your patience.

A/Prof Mark Sonderup: My main supervisor from conception of this project to submission. Prof Sonderup guided me through the entire process from proposal, ethics approval, data analysis and revision of the write up.

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Dr Kevin Rebe: Dr Rebe was very instrumental in design of this study protocol and more especially the questionnaire. He assisted a lot with data collection and he gave his final input prior to our submission.

Mr. Tawanda Chivese: Tawanda's contribution to this study was invaluable, he assisted with recruitment and data collection. He helped a lot with with statistical analysis and write up. He approved the final submission.

Chapter 2: Journal Publication

Title: Hepatitis C prevalence in HIV-infected heterosexual men and men who have sex with men

Authors: N A Gogela [1], M W Sonderup [1], K Rebe[2], T Chivese [3, 4], C W Spearman [1]

Affiliations:

1. Division of Hepatology, Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
2. ANOVA Health Institute, Johannesburg and Cape Town, South Africa
3. Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.
4. Biostats Unit, Centre for Evidence Based Health Care, Department of Global Health, University of Stellenbosch, Faculty of Medicine and Health Sciences, Cape Town, South Africa

Corresponding author:

Name: Professor Mark Sonderup
Email: mark.sonderup@uct.ac.za
Address: Division of Hepatology,
Department of Medicine, Faculty of Health Sciences, UCT and Groote Schuur Hospital, Observatory, CT, RSA, 7925.
Telephone: +27214043540

ABSTRACT

Background: Globally 1% of individuals are infected with hepatitis C virus (HCV). In South Africa (SA), the prevalence ranges between 0.3% - 1% with few prospective screening data available. Similarly, local data on transmission modes of HCV are limited but probably include parenteral routes and pre-1992 blood or blood product products. The risk of heterosexually transmission is low but is increased in men who have sex with men (MSM) with co- transmission risk of both HIV and HCV.

Objectives: Given a limited local understanding, we sought to better understand HCV characteristics and prevalence in 2 groups of HIV-infected men.

Methods: HIV positive men in the greater Cape Town metropolitan area were recruited. Sexual orientation was self-identified and demographic and other personal data obtained via a confidentially administered questionnaire. Participants were screened for HCV after a blood draw and positive HCV Ab tests were tested for HCV RNA. Risk factors associated with HCV seropositivity were determined.

Results: Five hundred HIV positive men were recruited; 215 (43%) non-MSM and 285 (57%) MSM, with median age 36 years (IQR 20 – 64) and 37 years (IQR 21 – 56), in the MSM and non-MSM group, respectively, *p* = NS. Overall, 3.4% (n=17) screened HCV positive, 5.6% (n=16) MSM and 0.5% (n=1) non-MSM, with 82.4% viremic for HCV RNA. In respect to genotype (GT) distribution, 50% were infected with GT1, 14.3% GT4 and 35.7% were GT2. In terms of risk, MSM were more likely to have used drugs (54.4% vs. 30.2%, p<0.001) and to have used all five modes of drugs administration (13% of MSM vs. 0.5% of non- MSM for injected drugs, 36.1% vs. 2.3% inhaled, 10% vs. 0% for the rectal route, 48.1% vs. 28.8% for smoked and 27.4% vs. 2.3% for oral drugs). More MSM than non-MSM (46.3% vs. 16.7%) reported sex whilst using recreational drugs and similarly more MSM (21.4% vs. 14%) reported having sex with a sex worker (SW).Risk factors for HCV seropositivity included drug use history (odds ratio (OR) 6.28, 98% confidence interval (CI). 1.78 – 22.12: p=0.004) and in MSM , sex with SW (OR 5.5, 95% 2.06 – 14.68; p=0.001) or use of recreational drugs with sex (OR 6.88, 95% CI 2.21 -21.44; p=0.001).

Conclusion: HCV prevalence in HIV positive MSM is higher than previously appreciated or documented in South Africa. Risk factors include injecting drug use, use of recreational drugs with sex and sex with SWs. Targeted interventions are required to address this emerging challenge to achieve the viral hepatitis elimination ideal by 2030.

INTRODUCTION

In 2017, an estimated 71 million people globally were hepatitis C virus (HCV) viremic while 2.3 million HIV co-infected (1). HCV is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) (2). Traditionally, HCV transmission has mostly been parenteral, typically in people who inject drugs (PWID) but recent data from have demonstrated that HCV prevalence increased by 15 - 20% in HIV infected men who have sex with men (MSM) between 2007 and 2008 (3). Supporting these findings are reports from the United States, Australia and Eastern Europe of HCV emerging as a sexually transmitted infection amongst MSM. Data from the UK Public Health Service in 2012 noted HIV notifications increasing by 24% amongst MSM of which 13% were HCV co-infected (4). In 2015, HCV accounted for almost 38 000 deaths in sub-Saharan Africa(5). However, data are few for high-risk groups with accurate data collection complicated by potential cultural bias and laws against PWID and men who have sex with men (MSM). Approximately 8% of the global PWID population resides in sub-Saharan Africa and hepatitis C is incompletely characterized in this key population(6)

The genotype distribution of HCV in a population is informative and the finding of predominantly genotypes 1 and 4 in non-PWID MSM and genotype 3a amongst PWID suggests intra-network modes of transmission (7).

South Africa is an epicentre of the HIV pandemic with an estimated 12.2% HIV prevalence equating to some 7.1 million HIV infected people(8). There are very few data on HCV and HCV- HIV co- infection In South Africa. Data from blood transfusion services, reports donor HCV viremic rates of ≤0.3% and random clinic-based data reporting 1% sero-prevalence rates. Interestingly, in a 1997 antiretroviral therapy study with mandatory HCV screening that included South Africa, HCV Ab prevalence in HIV positive patients, was 2%(9). This was much higher than previously anticipated. Local HIV management guidelines do not recommend the routine screening for HCV. A concern with HIV/HCV co-infection is that it can accelerate the progression of liver disease and HCC risk(10).

OBJECTIVES:

Given a need for the better understanding of our local HCV epidemiology, we elected to determine local HCV prevalence in an at-risk group viz. HIV positive men, by comparing heterosexual and MSM, so as to better understand and identify modes of transmission and HCV genotype distribution.

METHODS

Study Design

Serologically confirmed HIV positive men aged > 18 years, were prospectively recruited between 2011 and 2014 from health care centres within the greater Cape Town metropolitan area, including a dedicated clinic serving MSM. Following informed consent, participants self-identified their sexual orientation as heterosexual or as a man who has sex with men. A confidential questionnaire was administered during a face-to-face interview. Blood samples were obtained for testing and storage at -80^{o}C within an hour of collection. Serum was tested for the presence of hepatitis C IgG-antibody using the ARCHITECT II system (**Abbott** Diagnostics Division). Positive samples for hepatitis C IgG antibody were analysed for the presence of hepatitis C RNA by means of an in-house PCR technique after amplifying the 5'NCR region of the virus. HCV genotype was determined using the Versant HCV genotype v2.0 Line Probe Assay (Siemens AG) and viral loads using the COBAS Ampliprep/Cobas TaqMan v2.0 (Roche Diagnostics). All participants identified to be positive for HCV, were referred to the Liver Clinic at Groote Schuur Hospital, Cape Town. The Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town approved the study (HREC # 355/ 2009) and complied with the Declaration of Helsinki (2007).

Data collection

A standardized structured questionnaire that included demographic data was administered to all participants to capture information on age, self-identified ethnicity/race, self-identified sexual orientation and other potential risks factors for HCV acquisition e.g. previous blood transfusion or blood products received prior to 1992. A detailed history of past or current substance use was obtained including cannabis, MDMA (Methylenedioxymathampetamine), GHB (Gamma-Hydroxybutyrate), crystal

methamphetamine, cocaine, CAT (Methcathinone), heroin and methaqualone. The mode of substance use administration was recorded as oral, sniffing/insufflation, injection, smoking or rectal and the quantity of alcohol consumed (grams per day) was also documented. Information as to the use of these substances times of sexual intercourse in addition to the use of commercial sex worker services was also recorded. Additional data included possible needle-stick injury (especially for health care workers) and known hepatitis B surface antigen status and CD4 counts were documented.

Statistical analysis

The non-MSM and MSM groups were compared and statistical significance was tested at a level of 0.05 and 95% confidence intervals. Medians and interquartile ranges were reported for measured data (age and CD4 count) as they were not normally distributed while frequencies and percentages were used to describe categorical data. The x^2-test was used to compare categorical outcomes with the Wilcoxon-rank-sum test used to compare measured data. HCV prevalence as reported by antibody and viremia was calculated as a simple proportion of HCV positives divided by the whole sample.

Exploratory univariate analysis for factors associated with acquiring HCV infection was performed. Blood transfusion and a history of drug use were considered as possible risks for acquiring HCV. The use of individual drugs (cannabis, MDMA, GHB/liquid E, crystal methamphetamine, cocaine, CAT, heroin and methaqualone) and drug administration modes (oral, sniffing, injection, smoking and rectal) were also explored for association with acquiring HCV. Other variables considered were previous parenteral injury for former or current health care workers, sexual history variables such as whether they were in a current relationship or not, current sex partner, MSM vs. non-MSM, drug use before or during sex and sex with a commercial sex worker. Odds ratios and their 95% confidence intervals were reported.

RESULTS

Demographic Characteristics

Table 1 provides a summary of the demographics of the study participants. Of the 500 HIV positive men recruited, 285 (57%) were MSM and 215 (43%) non-MSM. The median age of the MSM and the non-MSM were 36 years (IQR 20 – 64) and 37 years (IQR 21 – 56), (p=NS). The CD4+ T- cell count, of MSM was significantly higher than the non-MSM group; 413 cells/μL (IQR 78-989)vs. 283 cells/μL (IQR 7-727), respectively; *p<0.001.,*

Most non-MSM participants were Black African (88.8%) while most of MSM (48.1%) were White. There were no differences in pre-1992 blood or blood product exposure between MSM and non-MSM. MSM were more likely to have used drugs compared to non-MSM; (54.4% vs. 30.2% p<0.001). Furthermore, MSM were more likely to have used all five modes of drugs administration compared to non-MSM, p<0.001. MSM were also more likely to have used cannabis, GHB, MDMA, crystal meth, cocaine, CAT or heroin. No participants gave a history of a needle stick injury.

Non-MSM were more likely to be in a monogamous relationship compared to MSM, 76.3% vs. 42.1%, p<0.001. A small component of MSM (2.3%) reported women as their predominant sexual partners while 7.8% reported having both male and female as their normal sexual partners. Of the MSM, 46.3% reported having sex under the influence of recreational drugs compared to 16.7% of non-MSM (p<0.001), while 21.4% of MSM reported having sex with a commercial sex worker compared to 14% of non-MSM, p=0.033. Significantly more non-MSM than MSM, 26.1% and 18.3%, respectively, reported alcohol consumption of ≥40 grams per day, p= 0.036. Hepatitis B surface antigen status did not differ significantly between MSM and non-MSM, (p= 0.064).

Hepatitis C virus prevalence

In total, 3.4% (n=17) were HCV IgG-antibody positive at screening (see Table 2), the majority in the MSM group (5.6% of MSM (n=16) and 0.5% in the non-MSM group(n=1). Non-MSM who screened HCV antibody positive, reported only inhaled heroin use and no other drug use. Of the MSM who screened positive, 14 were HCV PCR positive and 3 tested negative, yielding a viremia rate of 2.8%. In respect of genotype (GT) distribution, 50% were GT1, 14.3% GT4 and 35.7% were GT2 infected. The median HCV viral load was reported at 538

500 IU/ml (range 19000 – 1 400 000]. Of those who screened HCV positive, a single participant reported using a significant amount of alcohol (≥40 grams/day).

Risk factors for HCV

Factors associated with increased risk of acquiring HCV infection are listed in Table 3. White race, low CD4+ count and use of drugs were strongly associated with risk. This was irrespective of the type of drug used or route of administration. Use of drugs with sex and sex with a SW were associated with equal risks of being HCV- positive.

DISCUSSION

The overall HCV seroprevalence in HIV –positive men was of 3.4%, notably higher than what previously reported in SA. However, MSM constituted the vast majority of those that screened HCV-antibody positive. This is in keeping with data supporting MSM as an emerging at-risk population. Our study is the first prospective screening study of its kind in South Africa specifically looking at this key demographic. A recent systematic review of HCV seroprevalence in the sub-Saharan Africa region suggested a pooled HCV seroprevalence rate of 2.98%. When sub–categorized, the HCV seroprevalence rate was 5.7% among HIV infected individuals (5) (11). Our findings are thus not that dissimilar. Two studies in Nigeria based on hepatitis C antibody seroprevalence in different centers, 3 years apart and performed in a heterogeneous groups of HIV positive cohorts, demonstrated even higher seroprevalence rates of 10.8% and 15% respectively (12, 13,). Interestingly more women tested HCV antibody positive. In one of the studies, there was no significant correlation between injecting drug use and HCV infection (13). This possibly suggests that HIV poses a significant risk for HCV acquisition regardless of gender. In this cohort, it is unclear whether the women were asked about their sexual risks or whether they were screened for other sexually transmitted infections.

In those who were HCV antibody positive, 82% confirmed HCV RNA –positive, yielding an overall viremic rate of 2.8%. All our viremic patients were in the MSM cohort. We observed that MSM were more likely to use drugs compared to non-MSM and more significantly MSM used the injection route more frequently compared to the non-MSM. Existing data supports the fact that injecting drug use is associated with greater risks of both HIV and HCV

acquisition (14). All participant in the MSM group who tested HCV antibody positive had a history of injecting drug use amongst other routes. The single non- MSM participant denied injecting drug use.

An important factor associated with risk of HCV acquisition was high risk sexual behaviour. There were significant differences in numbers of MSM who engaged in such behavior, namely, having unprotected sex with commercial sex workers and having sex under the influence of recreational drugs. Several studies have shown that HCV is increasing as a sexually transmitted infection among MSM who do not inject drugs (16/17). Several observational studies comparing injecting to non-injecting MSM and observed that the non-injecting patients had different viral phylogenetic profiles compared to the injectors (18-20). The conclusion from this observation suggested a per mucosal route of transmission especially among HIV positive MSMs who have multiple sexual partners, MSM who tested positive for other sexually transmitted disease namely syphilis and MSM who engaged in traumatic sexual practices like fisting and use of objects. Similarly, we observed an association between sex with SW and HCV seropositivity. We observed that injecting drug users were seven times more likely to acquire HCV infection compared to non-injecting drug users. It is however thought that more traumatic sexual behaviours increase the risk of HCV transmission (21). These behaviours include lack of lubricant use, possible douching before anal sex, multiple partners and sex in the context of crystal methamphetamine use. We did not record such information on the specific sexual practices of MSM in our study other than the determination of anal sex practices. We do however note that in our local experience, we have observed several HCV positive MSM without any reported substance use or behaviours likely to be traumatic to ano-rectal tissue, suggesting ordinary unprotected penile-anal sexual activity as the only risk factor for HCV transmission, in often concomitantly HIV positive MSM (22).

An unexpected finding was the genotype distribution in our cohort. Genotype 1a predominated (50%), followed by genotype 2 (35.7%) and genotype 4 (14.3%) with no genotype 3 or 5 reported. This contrasts with a study in the general South African population, where even though genotype 1 was the most dominant genotype among blood donors (34%), genotype 5 was the most prevalent in overall population (5). However, a very

recent seroprevalence survey of key populations in SA demonstrated genotypes 1,3 and 4 in MSM, PWID and SWs(23). This suggests that selected genotypes are circulating in South African MSM, and other key populations. Furthermore, given that Cape Town is a popular international destination, the possibility of sex tourism by MSM introduces the potential that dominant genotypes, e.g. genotype 2c from European origins may explain this genotype predominating in our MSM population. Phylogenetic linkage analysis of patients with similar, yet uncommon genotype subtypes would suggest a network spread of virus. Seven out of fourteen viremic patients have been linked to care. They were all treated successfully – 1 with pegylated interferon/ribavirin based therapy and all others with the more recent hepatitis C direct acting antiviral therapies. Despite proper counselling during the recruiting period, 68% of HCV viremic individuals were lost to follow-up and appropriate linkage to care. This has serious implications; these are high-risk individuals who are likely to onwardly transmit the infection. Hepatitis C is invariably an asymptomatic infection and if high-risk individuals are not screened periodically, we will fail to identify and treat HCV-infected individuals and prevent onward transmission. Elimination of viral hepatitis in the high-risk groups of MSM and PWID requires active harm reduction practices including hepatitis B vaccination, condom usage and needle-syringe and opiate substitution programmes.

Study limitations

This was a small select group that lacked heterogeneity. A larger number that is more representative of South Africa that will include provinces that are more affected by HIV infection might yield different HCV seroprevalence rates.

Conclusions

This study alone does raise concerns that HCV seroprevalence is indeed underestimated in South Africa in at risk populations. Key populations, and particularly those who are HIV – infected, should access HCV screening. Furthermore, all patients with risks profiles as described above should be tested for HCV and be linked to care. Without addressing infections in key populations, attainment of the elimination ideal for hepatitis C will not be achieved.

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Author contributions. MWS conceived the study, NAG and TC executed the field work for the study in participant recruitment and prepared the draft manuscript. All authors contributed to the development of manuscript and final submission.

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Conflicts of interest. None

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Table 1: Characteristics of MSM and non-MSM participants

Variable	MSM (N= 285)	Non-MSM (N= 215)	*P value*
Age (Median; IQR) [years]	36 (20 – 64)	37 (21 – 57)	*0.627*
CD4 count (Median; IQR)	412.5 (78 – 989)	283 (7 – 727)	*<0.001*
Ethnicity; n (%)			*<0.001*
• Mixed Ancestry	66 (23.2)	18 (8.4)	
• Black African	79 (27.7)	191 (88.8)	
• Whites	137 (48.1)	5 (2.3)	
• Asian	3 (1.1)	1 (0.5)	
Blood transfusion (Pre-1992), (%)	2.8	0.9	*0.138*
Drug history (Yes) (%)	54.4	30.7	*<0.001*
Drug routes (%)			
• Injected	13.3	0.5	
• Oral	27.4	2.3	
• Smoked	48.1	28.8	
• Inhaled	36.1	2.3	*<0.001*
• Rectal	10.2	0	
Drug usage (%)			
• Cannabis	39.7	27.4	*0.004*
• MDMA	29.8	2.8	*<0.001*
• GHB/Liquid E	17.9	0.9	*<0.001*
• Crystal Meth	31.9	4.2	*<0.001*
• Cocaine	30.9	3.7	*<0.001*
• CAT	39.7	27.4	*<0.001*
• Heroine	7.0	2.8	*0.035*
• Mandrax	6.7	6.5	*0.945*
In a current relationship (Yes, %)	42.1	76.3	*<0.001*
Had sex under influence (Yes, %)	46.3	16.7	*<0.001*
Had sex with commercial sex worker (Yes, %)	21.4	14.0	*0.033*
Normal sex partner			
• Men	90.1	0	
• Women	2.1	100	*<0.001*
• Both	7.8	0	
Alcohol intake >40g/day (Yes, %)	18.3	26.1	*0.036*
Hepatitis B surface antigen			
• Positive	4.9	2.8	*0.064*
• Negative	67.4	47.9	
• Unknown	27.7	49.3	

IQR: Interquartile range; MDMA: Methylenedioxymethamphetamine; GHB: Gamma-Hydroxybutyrate; Meth: Methamphetamine; CAT: Methcathinone

Table 2: Hepatitis C infection prevalence

	Number screened positive	Prevalence (95% CI)
All participants (n = 500)	17	3.4% (2.1 – 5.4)
MSM (n = 285)	16	5.6% (3.5 – 9.0)
Non-MSM (n = 215)	1	0.5% (0.06 – 3.3)

MSM: Men who have sex with men

Table 3: Risk factors for HCV infection: Univariate and Multivariate analyses

Variable	Univariate Analysis	
	OR (95% CI)	**P-value**
Demographics		
• Age	1.04 (0.995-1.09)	0.078
• Ethnicity (Black African)	1 (base)	
• Ethnicity (Mixed Ancestry)	3.24 (0.20-52.38)	0.408
• Ethnicity (White)	31.77 (4.15-243.18)	0.001
• CD4 count	1.003 (1.001-1.005)	<0.001
Drug use		
• Drug use history	6.28 (1.78-22.12)	0.004
• Using cannabis	3.67 (1.33-0.09)	0.012
• Using MDMA	4.28 (1.61-11.43)	0.004
• Using GHB	6.65 (2.42-18.30)	<0.001
• Crystal meth use	10.77 (3.70-31.36)	<0.001
• Cocaine use	3.99 (1.50-10.63)	0.006
• Using CAT	7.64 (2.84-20.54)	<0.001
• Heroin use	9.17 (2.96-28.41)	<0.001
• Mandrax use	3.24 (0.88-11.88)	0.077
Drug use Routes		
• Smoking	5.19 (1.67-16.15)	0.004
• Injection	22.35 (7.93-63.04)	<0.001
• Nasal	7.30 (2.63-20.22)	<0.001
• Oral	6.22 (2.32-16.63)	<0.001
• Rectal	7.97 (2.60-24.45)	<0.001
Alcohol ≥ 40grams /day	0.22 (0.29-1.68)	0.144
Sexual History		
In a current relationship	0.40 (0.14-1.11)	0.077
Current partner (Both)	1(Base)	-
Current partner (Female)	Omitted	-
Current partner (Male)	1.07 (0.38 - 2.97)	0.897
MSM (vs non-MSM)	12.73 (1.67-96.75)	0.014
Sex after drugs	6.88 (2.21-21.44)	0.001
Sex with CSW	5.50 (2.06-14.68)	0.001
Normal sex partner	0.23 (0.07-0.77)	0.018
Hepatitis B surface antigen (positive vs negative)	1.53 (0.56-4.17)	0.405

MDMA: Methylenedioxymethamphetamine; GHB: Gamma-Hydroxybutyrate; Meth: Methamphetamine; CAT: Methcathinone; MSM: Men who have sex with men; CSW: Commercial sex worker

APPENDICES

APPENDIX 1: LETTER FROM THE EDITOR AND REVIEWERS' COMMENTS

From: "SAMJ" <em@editorialmanager.com>
Date: 14 December 2017 at 09:39:05 SAST
To: "Mark W Sonderup" <msonderup@samedical.co.za>
Subject: Decision on your Submission to SAMJ
Reply-To: "SAMJ" <submissions@hmpg.co.za>
Ref.: SAMJ13041
Hepatitis C prevalence in HIV-infected heterosexual and men who have sex with men
South African Medical Journal

Dear Professor Sonderup,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript.

For your guidance, reviewers' comments are appended below.

If you are prepared to undertake the work required, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by Jan 11, 2018. Please let us know if you require additional time.

To submit a revision, go to http://samj.edmgr.com/ and log in as an Author. You will see a menu item called Submission Needing Revision.

Best wishes

Bridget Farham, PhD
Editor
South African Medical Journal

Reviewers' comments:

Reviewer's Responses to Questions

Please comment on your General impression of this manuscript - bear the following in mind:

Is the article relevant?

Does it offer anything new?

Are there similar studies in our region/outside the region?

Does it add to the existing medical body of knowledge?

On first glance, are the methods, results and conclusions reasonable?

Do the conclusions actually draw on the results?

Does the article have a clear message?

Will it help SAMJ readers make better clinical decisions and, if so, how?

Is a general medical journal the right place for it?

Reviewer #1: This study aims at better understanding HCV prevalence in HIV-coinfected males from South Africa. Indeed, there is very little data on HCV prevalence among HIV positive individuals from this region. The authors quite interestingly found an HCV seroprevalence of 3.4% and a viraemic rate of 2.8% among a group of HIV positive men, which is far higher than previously reported in South Africa and underlines that HC screening should be universally done in anyone who comes down with an HIV diagnosis. This is of particular importance as DAA therapies start to roll out promising HCV cure in over 95% of viraemic patients. Some issues need to be addressed, however. First, studies assessing HCV antibody positivity only may suffer from false positive results so need to be regarded critically and clearly combination of HCV ab and RNA examinations are required. Reference 14 for example only used SWE-life HCV ultra-rapid test strip for antibody detection. This needs to be reflected in the discussion. For reference 15 the journal cited seems to be wrong. The correct citation should be BMC Infect Dis. 2012; 12: 130. With regard to sexual transmission risk it has been discussed that the very low risk for HCV transmission in heterosexuals versus the increased rate of transmission of HCV in MSM results from sex practices with increased risk for sexual practices with blood-blood contacts in particular unprotected anal intercourse and fisting. Could the authors say something more specific about the sexual practices among the MSM included as this could help shed light on HCV transmission risk. Considering the rather unusual distribution of genotypes could it be that some of the MSM related infections were acquired outside of Africa for example in Berlin or London. This should be discussed because GT1 id the dominant GT of the European outbreak of HCV among MSM.

Please comment on the Methods and analysis presented in this manuscript

Study design

Is the research question and planned outcomes clearly defined?

Was the sample adequate and sufficiently described?

Are the methods adequately described and appropriate to the study objectives?

Statistical considerations

Are simple statistical methods applied appropriately?

Reviewer #1: Methods are ok except more specific information on sexual practice would be required.

Please comment on the Results, Discussion and Conclusions presented in this manuscript

Results

Is the population/sample adequately described?

Are the results clearly presented?

Are they credible and do they answer the research question?

Are tables clear and useful, not simply mirroring data discussed in the Results text?

Reviewer #1: This study aims at better understanding HCV prevalence in HIV-coinfected males from South Africa. Indeed, there is very little data on HCV prevalence among HIV positive individuals from this region. The authors quite interestingly found an HCV seroprevalence of 3.4% and a viraemic rate of 2.8% among a group of HIV positive men, which is far higher than previously reported in South Africa and underlines that HC screening should be universally done in anyone who comes down with an HIV diagnosis. This is of particular importance as DAA therapies start to roll out promising HCV cure in over 95% of viraemic patients. Some issues need to be addressed, however. First, studies assessing HCV antibody positivity only may suffer from false positive results so need to be regarded critically and clearly combination of HCV ab and RNA examinations are required. Reference 14 for example only used SWE-life HCV ultra-rapid test strip for antibody detection. This needs to be reflected in the discussion. For reference 15 the journal cited seems to be wrong. The correct citation should be BMC Infect Dis. 2012; 12: 130. With regard to sexual transmission risk it has been discussed that the very low risk for HCV transmission in heterosexuals versus the increased rate of transmission of HCV in MSM results from sex practices with increased risk for sexual practices with blood-blood contacts in particular unprotected anal intercourse and fisting. Could the authors say something more specific about the sexual practices among the MSM included as this could help shed light on HCV transmission risk. Considering the rather unusual distribution of genotypes could it be that some of the MSM related infections were acquired outside of Africa for example in Berlin or London. This should be discussed because GT1 id the dominant GT of the European outbreak of HCV among MSM.

Discussion

Are the results well discussed in light of previous evidence and the literature?

Are the limitations of the study sufficiently discussed? / Are the strengths and weakness discussed?

Is the meaning and relevance of the study discussed?

Reviewer #1: Not all citations are correct and some articles need to be discussed more critically.

Conclusion

Are the implications of the research summarised?

Do the authors make relevant recommendations for future research or application?

Reviewer #1: yes, addressed adequately.

Reviewer #1: This study aims at better understanding HCV prevalence in HIV-coinfected males from South Africa. Indeed, there is very little data on HCV prevalence among HIV positive individuals from this region. The authors quite interestingly found an HCV seroprevalence of 3.4% and a viraemic rate of 2.8% among a group of HIV positive men, which is far higher than previously reported in South Africa and underlines that HC screening should be universally done in anyone who comes down with an HIV diagnosis. This is of particular importance as DAA therapies start to roll out promising HCV cure in over 95% of viraemic patients. Some issues need to be addressed, however. First, studies assessing HCV antibody positivity only may suffer from false positive results so need to be regarded critically and clearly combination of HCV ab and RNA examinations are required. Reference 14 for example only used SWE-life HCV ultra-rapid test strip for antibody detection. This needs to be reflected in the discussion. For reference 15 the journal cited seems to be wrong. The correct citation should be BMC Infect Dis. 2012; 12: 130. With regard to sexual transmission risk it has been discussed that the very low risk for HCV transmission in heterosexuals versus the increased rate of transmission of HCV in MSM results from sex practices with increased risk for sexual practices with blood-blood contacts in particular unprotected anal intercourse and fisting. Could the authors say something more specific about the sexual practices among the MSM included as this could help shed light on HCV transmission risk. Considering the rather unusual distribution of genotypes could it be that some of the MSM related infections were acquired outside of Africa for example in Berlin or London. This should be discussed because GT1 is the dominant GT of the European outbreak of HCV among MSM.

APPENDIX 2: JOUNAL INSTRUCTION TO AUTHORS

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.

To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website:

www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

Research
Reviews
Clinical trials
Editorials
In Practice (Previously Forum incl. Case Reports)
Correspondence
Obituaries
Book reviews
Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

Guest editorial
Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R7 500 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publicaiton fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.
Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an

article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structuresto ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchershave been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ.*

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Noncommercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of

publication. The **Author Agreement form** should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

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.

Here is an example of a good abstract.

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.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

Case report
Clinical practice
Clinical alert
Issues in medicine
Issues in public health
Healthcare delivery
Consensus/Position statement
Medicine and the environment
Medicine and the law
Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant

- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

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
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  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

  - Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

  - Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

  - Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

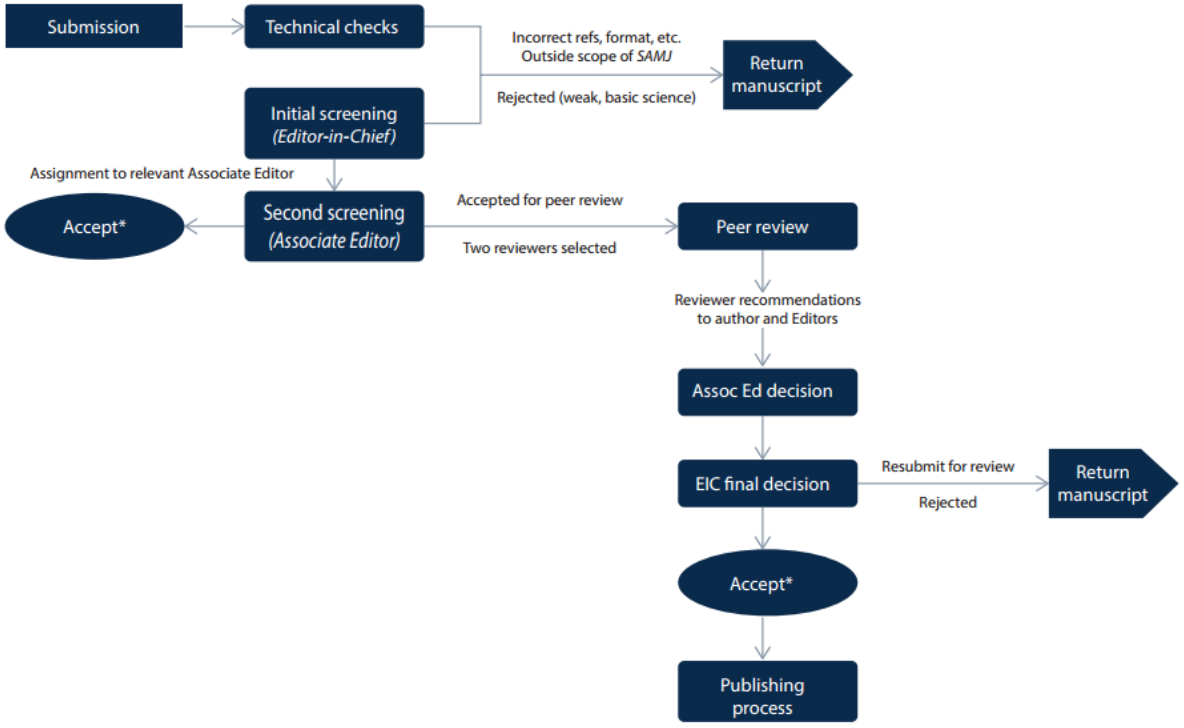
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - **Author Agreement form**
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts, CME
**Some minor revisions may be requested

Production process

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
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7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

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Online

- The full text of all accepted articles is published in full online, open access, within 4 - 6 weeks of acceptance.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

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- Scopus
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5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
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