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REVIEW

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Access to generic medicines for hepatitis C in South Africa: a journey of discovery

Mark W. Sonderup, Catherine Wendy Spearman

Division of Hepatology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town - South Africa

ABSTRACT

The true seroprevalence of hepatitis C in South Africa is not clear, with some data suggesting a high prevalence in key subpopulations. While genotype 5 infection is highly prevalent, all other genotypes (except genotype 6) are seen, making it a pan-genotypic country. With the advent of direct-acting antiviral (DAA) therapy, patient demand for access has grown. In a country with a high GINI co-efficient, affordability – as with antiretroviral therapy – was always going to be a major factor. No clear route to access these therapies existed, and at listed USA and European prices, were out of reach to most, if not all, for most, if not all, patients in South Africa. A single patient, albeit in a potentially hazardous manner, and of his own accord, made his own DAA therapy by purchasing raw active pharmaceutical ingredients and filling capsules. Unsurprisingly, when the treatment failed, the patient turned to us for assistance. Consequently, he led us to generic therapies, and through the correct processes we accessed care for him. It was this act that opened up a channel for us to assist many other patients. In time, access to lower prices for some originator DAA therapies has materialized; however, to many, this still may be out of reach. Generic medicines for hepatitis C do work and are effective and affordable. If we are going to achieve the objective of the elimination of viral hepatitis, generic medicines will need to form part of the solution.

Keywords: Medicine access, Generic medicines, Hepatitis C, South Africa

The unique aspects of hepatitis C in South Africa

The true nature of hepatitis C seroprevalence in South Africa is not clear. Existing data suggest low general prevalence with some data indicating a very high prevalence in vulnerable populations (e.g., people who inject drugs). In a country with an extremely high burden of HIV, the need to identify and treat those who are infected with hepatitis C is important to avoid an additional health care challenge on an already burdened health care system.

A complete understanding of the real prevalence of hepatitis C in South Africa does not exist. Blood bank data serially point towards it being a low prevalence co untry, but available data are conflicting and disparate, ranging between 0.08% and 1.7% (1, 2). However, seroprevalence data from blood donors may be a suboptimal reflection of the true prevalence given the inherent, albeit appropriate, barriers in place to ensure a safe blood supply (2, 3). While seroprevalence in the general population is estimated at approximately 1%, data are emerging that suggest significantly higher prevalence in vulnerable key populations. Unsurprisingly, seroprevalence rates of 40%-60% are being reported in cohorts of people who inject drugs (PWID) from metropolitan areas, such as the capital city, Pretoria, while a seroprevalence of 6% has been observed in Cape Town in men who have sex with men (4). Currently, a large study is being conducted serosurveying key vulnerable populations in South Africa. This study will provide better data on the seroprevalence rates in these high risk subpopulations. Another intriguing aspect is the epidemiology of hepatitis C in South Africa. While vulnerable populations pose an obvious risk for hepatitis C acquisition (e.g., PWID), many patients do not have such a risk. In fact, compared to many other countries, the overall rate of injecting drug use is low and it only accounts for about 8% of hepatitis C in sub-Saharan Africa, with South Africa being similar in this regard (5). In our own experience, blood or blood product exposure prior to 1992 accounts for about 30% of our hepatitis C patient population, who are often either hemophiliacs or women who received blood as a result of postpartum hemorrhage. Other risks, in our experience, include PWID, health care workers with percutaneous needle stick injuries, and, rarely, perinatal mother to child transmission. There is a significant number of patients (approximately 25%) who have no clear definable risk factor. South Africa is an ethnically and culturally diverse country. A measure of this

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Corresponding author:
Professor Mark W. Sonderup
Division of Hepatology, Department of Medicine
Faculty of Health Sciences
University of Cape Town
Observatory
7925 Cape Town
South Africa
msonderup@samedical.co.za

diversity is that, since 1994, our Constitution has allowed for 11 different languages – all with equal status. Many South Africans have diverse cultural practices, including ritual circumcision, traditional scarification, and other activities that pose a potential risk for horizontal hepatitis C transmission. These are intriguing as they are difficult to quantify for transmission risk. The epidemiological aspects of hepatitis C transmission in South Africa and sub-Saharan Africa share similarities with high-income countries, but do not fully mirror all aspects of transmission risk.

Another important issue is that South Africa is a "pan-genotypic" country. While it is home to the unique genotype 5 hepatitis C virus (HCV), genotypes 1-4 occur frequently. Hepatitis C genotype data from 1995 have suggested that genotype 5 accounted for 39.2%, genotype 1: 33%, genotypes 2 and 3: 21.5%, and genotype 4: 2.3% (6). A recent study that looked at more than 1,000 patients from across South Africa reconfirmed that we are a pan-genotypic country (7). Again, genotype 5 was predominant at 35% followed by genotype 1: 31%, genotype 2: 2%, and genotype 3: 14%. Interestingly, genotype 4 increased to 14% from previous lows and may reflect the increase in immigrants from Central Africa who migrated to South Africa over the last 20 years.

Treatment of hepatitis C in South Africa

In 2002, Pegylated interferon (PEG-INF) and ribavirin became the standard of care for hepatitis C in South Africa. Drug registration only occurred several years later, and initially, several patients were treated through an expanded access compassionate use program. The numbers of patients treated in the first few years after registration in the private sector were few as most physicians chose to avoid having to use a complex treatment regimen with many adverse effects. Budgets for treating patients in the public sector eventually were set, and the treatment numbers increased. The patients most likely to benefit from PEG-INF and ribavirin-based therapy were preferentially selected for treatment, and the outcomes were very reasonable. However, the vast majority of patients did not access care, and it is likely that more than 5% of patients with hepatitis C were actively offered care or were treated. Another factor is that HIV-HCV co-infected patients seldom accessed treatment, given their poor response rates and increased toxicities.

With the advent of direct-acting antiviral (DAA) therapies, the first generation NS3/4A protease inhibitors, telaprevir and boceprevir, made their appearance. A handful of patients were treated with telaprevir-based therapy given its prohibitive cost and toxicities. In 2012, a 12-week course of telaprevir cost approximately US$22,000 making it unaffordable to patients in the public sector. In late 2013, sofosbuvir was registered in the USA by the Food and Drug Administration heralding a new era of hepatitis C management. Anticipation quickly turned to despair when we learnt of the US$84,000 price tag for 12 weeks of add-on treatment to PEG-INF and ribavirin. The INF-free era of therapy was clearly beckoning, and in early 2014 we wrote to our health minister appealing to him to take the lead in ensuring access to affordable treatment for our patients, not only in South Africa but also beyond our borders into sub-Saharan Africa. The basis of our argument was that, as a country, we had learnt enormous lessons from our HIV/AIDS disease burden and that similar intransigent approaches to ensuring affordable access should not be tolerated or accepted. Furthermore, the South African Government was a signee to the Doha Declaration of the World Trade Organization ensuring that the TRIPS Agreement (Trade-Related Aspects of Intellectual Property Rights) should be utilized to gain access to medications. To date, no response to our request has been received.

Generics clearly work, and the REDEMPTION-1 trial, presented at the 2016 European Association for the Study of Liver Disease meeting, demonstrated the efficacy of generic sofosbuvir/ledipasvir and sofosbuvir/daclatasvir (8, 9).

In mid-2014, Gilead Sciences indicated that they wished to lodge an application for registration of their products in South Africa. It was clear that retail prices in the USA and Europe would never be an option for a country such as South Africa, one of the most consistently unequal countries in the world with an income GINI coefficient ranging between 0.660 and 0.696 (10). Eventually, South Africa was added to the initial list of 91 countries that would get access to their product line for hepatitis C via their "International Access" program. However, Gilead did separate the public and private sectors in South Africa in terms of pricing. Sovaldi® and Harvoni® were priced at US$300 and US$400 per bottle, respectively, in the public sector and US$2,700 and US$3,500 per bottle, respectively, in the private sector. As no DAA therapies are registered in South Africa yet, all therapies were accessible via a named-patient process, which is a pre-registration legal procedure of obtaining a certificate from our medicines registering authority. While that constitutes an administration burden, the real issues that confronted us were the ability to access actual stock of the requisite medicines. This has proved to be considerably more challenging than anything else.

The vacuum created by the lack of any DAA being formally registered in South Africa created a space for any approved generic product to be used. While generics were an attractive and necessary option, we had never before engaged in such practice, and the practicalities of how to access such drugs were unclear. What follows is an amazing story of how patient power can lead the way many times.

The journey of a patient with hepatitis C

In November 2014, we received an email from a patient informing us of his story. At that stage he was unknown to us. He thought his story might help as he had read about us and some comments we had made in the media regarding DAA therapies. He was a businessman in his 60s, who had – quite by chance – asked his primary care doctor to check his "bloods" as he wasn't feeling his usual energetic self. A liver profile revealed elevated transaminases, and, in March 2014, a viral screen confirmed that he had a chronic HCV infection. It was confirmed as being a genotype 1b infection and his mode of likely acquisition was completely unknown. He was married, had no history of injecting drug use, but had undergone surgical procedures in the 1980s including an appendectomy and a hernia repair. He could not recall any blood or blood product use, and did not have any tattoos. He was referred to us for further management by his primary care doctor, but had defaulted and not attended his appointment. The patient was

resourceful and had done some reading – via Google – to note that the adverse effects of PEG-INF and ribavirin-based therapy were simply not going to work for him. What he also read was the January 2014 publication in the *New England Journal of Medicine* by Sulkowski et al entitled "Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection" (11). It was an open label phase 2 study of genotype 1, 2, and 3 patients with 12 or 24 weeks of sofosbuvir and daclatasvir. The patient thought he would do well in a self-assigned 12 week arm. Being a businessman running an import/export company, sourcing items was his forte. He immediately set about trying to source Sovaldi® and Daklinza™. He did, and the costs were astronomical – something he was unable to accept. Using Google, he tracked down a supplier of the active pharmaceutical ingredient (API) of both sofosbuvir and daclatasvir. He was determined to cure himself and was unhappy with what he read about drug prices. He flew to China and bought the API of both drugs paying US$17 per gram. He returned and filled 84 empty capsules approximately 400 mg of sofosbuvir and 84 empty capsules with 60 g daclatasvir, and proceeded to start the 12-week treatment under his own guidance, without any doctor or formal assessment of his degree of liver fibrosis. At 1 month, he checked his hepatitis C viral load and it confirmed a significant reduction to 798 IU/mL from a baseline of 6.5 million IU/mL. At the end of his treatment, his HCV load quantification (performed by Roche COBAS®, AmpliPrep/COBAS®, TaqMan®, HCV Qualitative Test, v2.0), was less than the lower level of quantification. In November 2014, armed with this information, he emailed and informed me of what had transpired. He did so in the hope that "it would help other patients." We understandably were concerned as pharmaceutical manufacture involves more than the API: a formulation is designed to enhance the bioavailability and absorption of a drug. However, it was clear that a drug was onboard, as the viral quantification tests had confirmed. We informed him of several issues. First, we could not participate in any activity that contravened regulations, and the law governing medicines and using drugs in such a manner was doing just that. Second, doing what he did was not advisable as one is never sure of the purity or grade of the API one is getting; it could actually be adulterated with toxic chemicals. Thirdly, confirmed viral eradication is only done 12-24 weeks after the end of treatment and this is what a sustained virological response (SVR) constituted. We advised that he repeat his viral testing in 3 months, and noted his fortitude and resourcefulness in wanting to simply cure himself of a chronic viral infection. However, the means were potentially harmful.

In February 2015, we received communication from the patient informing us that his hepatitis C viral load quantification was indeed positive again at 3.9 million IU/mL. We agreed to see him, and following a consultation, we set about determining the presence of resistance associated variants (RAVs) in his HCV. As anticipated, he remained fully sensitive to sofosbuvir but had developed several NS5A RAVs including the *Y93H* mutation. After reviewing him and confirming the absence of cirrhosis with a Fibroscan®, we advised 24 weeks of sofosbuvir and simeprevir. This time we advised against using self-constructed capsules of API. Simeprevir was obtainable, at a cost from the originator company, which the patient felt he could afford. What he could not afford was the cost of Sovaldi® at listed European or USA prices. Even with the announcement of the access program from Gilead, no mechanisms were in place to access stock, and there was no clear idea when this would happen. The patient's resourcefulness came to the fore again and he quickly advised me that we could access generic sofosbuvir from India as it had just been approved there the week before and was priced at US$300 per bottle. This indeed was true, and we set about going through the correct processes. A named patient certificate was obtained from our medicines regulatory authority to use unlicensed products, which were simeprevir (Olyssio®) and generic sofosbuvir from India. Relevant orders were placed and, seamlessly, the medicines arrived. The patient was commenced on sofosbuvir 400 mg and Olyssio® 150 mg daily. Treatment was uneventful and the patient achieved an SVR and has remained so in follow-up.

A pathway to accessing hepatitis C treatment

What the patient exposed was a channel to access generic therapies, and we have continued using this conduit. As incredulous, if not dangerous, as the patient's story is, his circuitous journey allowed us to find the pathways to subsequently access care for many of our patients. We have expanded our use to include generic sofosbuvir/ledipasvir and daclatasvir. The formal registration of all DAAs in South Africa is yet to happen, but the proverbial Pandora's box has been opened and people are being cured with generic DAAs.

Our medicines regulatory authority issues a named patient certificate for the use of a generic drug provided the pharmaceutical company that produces it has the relevant documentation confirming Good Manufacturing Practice. This does provide one with a degree of confidence in the quality control of these generics and mitigates against the oft quoted view that generics are less optimal than the original product. This notion was again recently put forward as an argument against the use of generic DAAs (12). It was debated that issues, such as bioequivalence studies, are inaccurate for the population in whom the therapy will be used, and that the absorption and elimination features of a given drug will change as the formulation of generic drugs are quite different. Also, accepted ranges of bioequivalence are not standardized. Other contrary points include aspects of drug quality whereby manufacturers can target cheaper or inferior quality APIs to limit costs. Packaging also may differ and influence tablet or capsule quality. While all these points may have relevance, generic sofosbuvir, sofosbuvir/ledipasvir, and daclatasvir are being manufactured under license to the originator companies by the pharmaceutical companies in India. Gilead licensed 11 generic manufacturers in India to now allow distribution to 101 countries globally (13). In April 2015, the WHO included daclatasvir in its essential medicine list, and in November 2015, Bristol-Myers Squibb allowed the Medicines Patent Pool to pronounce a license and technology transfer agreement for daclatasvir in 112 low and middle income countries allowing the manufacturing of generic daclatasvir globally (14). The effect is that relatively inexpensive generic products of sofosbuvir, ledipasvir/sofosbuvir, and daclatasvir are now available for countries to access. Furthermore, the supply chain is relatively seamless and stock is available.

Generic medicines are preferred over the originator products because of cost. An intriguing aspect is the pricing of originator drugs. What informed the US$84,000 price tag of Sovaldi®? Pharma companies argue that the cost of research and development (R&D) associated with new drug discovery is exorbitant. However, a 2012 review suggested this may not be the case and that costs of R&D are not quite those that are often suggested (15). So how was the cost of Sovaldi® and all the DAAs that followed thus determined if R&D is perhaps not such an issue? It is conceivable that the pricing was simply based on what was the "standard of care"; that is PEG-INF and ribavirin. Taking this into consideration, combined with the "cost of a cure," and simple market forces, pricing for 12 weeks was set at what was once referred to as "what people would pay," and that the price was justified considering the value. However, if the price of PEG-INF was used as a benchmark, then the pricing is founded on erroneous reasoning as the price of PEG-INF for hepatitis C was never correctly challenged. PEG-INF was never designed primarily for viral hepatitis; rather, its primary development was in oncology – an area where pricing is traditionally very high, and equally for many debatable reasons. When its therapeutic value was proven for hepatitis C, the pricing for its oncology use migrated to viral hepatitis. This should never have happened, and that error was simply perpetuated into the pricing of DAAs. This is an area that warrants transparent discussion as it may represent the core fallacious nature of the price structure of DAA therapies. What needs to be justly confronted is the current rapacious nature of pricing.

In South Africa, a paradoxical scenario currently exists where the pricing of some originator medicines is slightly cheaper than many generic medicines from India; therefore, in the public sector, originator products are preferred, except for daclatasvir, as the originator product is unaffordable. In addition, no pharma company has as yet lodged an application for daclatasvir registration, so we exclusively use a generic Indian product on a named-patient basis. Clear pricing has not yet been formally set for any other DAAs, including the products from AbbVie and Merck. The pricing of Olysio® has largely been set at the equivalent European prices. As noted, South Africa is a pan-genotypic country, so with available drugs, treatment of all genotypes is possible. The international access program of Gilead also means access to all current and future pipeline therapies at accessible prices. We await a formal pricing announcement for sofosbuvir/velpatasvir (Epclusa®).

As indicated, no DAA is formally registered by the medicines registering authority in South Africa. As the registering begins to happen, which is anticipated over the next year, the pipeline to generics will close as it will become illegal to use unregistered therapies for patients when a registered product is available. This is going to pose a problem for those who pay out of their own pocket or for privately funded patients, as they will be required to pay the set prices rather than accessing the significantly cheaper generic products. The power to overrule this lies with the government as it has the necessary legislative power to allow parallel importation as it has done with antiretroviral therapies. We eagerly wait to see what will happen now that Pandora's box has been opened. Reflecting on this journey to date, recognition must go to our patient who, in an albeit peculiar and potentially harmful process, was responsible for opening the box.

In sub-Saharan Africa we have an enormous task ahead to achieve the WHO objective of the elimination of viral hepatitis. Our experience to date suggests that many avenues are possible to access quality medicines. With respect to hepatitis C treatment in particular, which is a curable chronic infection, the quality of the medicine should be the only variable in accessibility – not the cost. It seems self-evident that access to treatment that cures a chronic viral infection is a fundamental human right, and if sub-Saharan African governments appreciate that, then we are already a long way into the journey.

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