MEDICO-LEGAL ISSUES RELATING TO PHARMACOGENOMICS AND THE DEVELOPMENT OF PERSONALISED MEDICINE IN THE CONTEXT OF HIV AND AIDS IN SOUTH AFRICA

by

ANGELA PATRICIA MOLUSI
STUDENT NUMBER: 6415954

Submitted in accordance with the requirements for the degree of

DOCTOR OF LAWS

at the

UNIVERSITY OF SOUTH AFRICA

Supervisor
Professor M. Labuschaigne

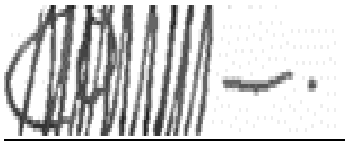
January 2023

Declaration

I, Angela Patricia Molusi (Student Number: 6415954), declare that:

Medico-legal issues relating to pharmacogenetics and the development of personalised medicine in the context of HIV and AIDS in South Africa

is my own work, and that all the sources that I have used or cited have been indicated and acknowledged by means of complete references.

Signature:  **Date:** **January 2023**

Angela Patricia Molusi

Dedication

This thesis is specially dedicated posthumously with love to my mother, Ellen Mmampolelo Makgopela who departed during the mid-stages of this work.

Acknowledgments

I express my most heartfelt gratitude to my Father in the Highest, Almighty God for His succour and grace throughout this research project, which would not have been possible with my human effort alone.

I am most indebted to my husband, Mogorosi Daniel Molusi, our two sons, Mpho and Otsile (particularly for their support and assistance with logistic); as well as daughters, Masego, Kelebogile and her husband, Thabo. I truly admire and appreciate your sacrifices, patience and steadfast support even beyond my expectations. I would not have made it without your deep commitment and continuous encouragement, all of which is propelled by your belief in my ability to complete this research project. Your unyielding dedication towards my success is highly treasured and irreplaceable.

My immeasurable appreciation to my supervisor, Professor M. Labuschaigne for your patience, perseverance, guidance, and relentless encouragement throughout the years. You are the best!!

Special thanks to Professors M.M. Mswela and M. Slabbert, my former colleagues in the Department of Jurisprudence at UNISA for sharing your publishing and writing skills experience with me. You are eternal treasures in my heart.

To Khothatso Mabasa, for your sharp eye and understanding mind that gave me such continuous and incredible support. You are a true delight to work with.

To Ms Refilwe Phala, my trusted and reliable library research guide. This thesis might never have been completed without your constant readiness and willingness to assist me in finding relevant references and sources both nationally and internationally.

To my editor, Dr Themba J. Mkhonto, your gut-level endurance and politeness were instrumental in enabling me to reach the submission deadline. You deserve special recognition.

I THANK YOU ALL, SO PROFOUNDLY!!

Abbreviations and Acronyms Used

ADRs	Adverse Drug Reactions
AHHHA	Africa Human Heredity and Health in Africa
AIDS	Acquired Immunodeficiency Syndrome
ARVs	Antiretroviral Drugs
ART	Antiretroviral Treatment
CDC	Centre for Diseases Control
CIOMS	Council for International Organisations of Medical Sciences
CIPRO	Companies and Intellectual Property Registry Office
DNA	Deoxyribonucleic Acid
DPA	Data Protection Act
EBM	Evidence-based Medicine
ECTA	Electronic Communications and Transactions Act 25 of 2000
EU	European Union
ECHR	European Court of Human Rights
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
HBM	Human Biological Materials
HICs	High-income Countries
HPCSA	Health Professions Council of South Africa
HRE	Human Research Ethics
HTA	Human Tissue Act 2004
ICESCR	International Covenant on Economic, Social and Cultural Rights
IPR Ac	Intellectual Property Rights
LMICs	Low and Middle-income Countries
MRSA	Medicines and Related Substances Act
MTA	Material Transfer Agreement
NDoH	National Department of Health
NACOSA	National Advisory Group on HIV/AIDS
NHA	National Health Act 61 of 2003
NHREC	National Health Research Ethics Council
NHS	National Health Service
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIPMO	National Intellectual Property Management Office
OECD	Organisation for Economic Co-operation and Development

PA	Patents Act 57 of 1978
PAA	Patents Amendment Act 20 of 2005
PGx	Pharmacogenetics and Pharmacogenomics
PAIA	Promotion of Access to Information Act 2 of 2000
PLWH	Persons Living with HIV and AIDS
PMTCT	Mother to Child Transmission
POPIA	Protection of Personal Information Act 4 of 2013
R&D	Research and Development
SAHPRA	South African Health Products Regulatory Authority
SAMA	South African Medical Association
SIV	Simian Immunodeficiency Virus
TAC	Treatment Access Campaign.
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UK	United Kingdom
UNESCO	United Nations Educational, Scientific and Cultural Organisation
WHO	World Health Organisation
WTO	World Trade Organisation

Definition of key terms/ concepts

Biobank: an organised collection of human biological material and associated data from different individuals, which are usually kept for an unlimited period of time for the purposes of health research.

Data: any directly or indirectly obtained personal and other information, in any form, and accrued during research undertakings or clinical care.

Pharmacogenetics: the scientific study of genes as a factor in pharmacology, and concerned with the effect of genetic makeup on reactions to drugs

Pharmacogenomics: the scientific study of complex multigene patterns within the genome which are examined in conjunction with the cause of adverse drug reaction.

Personalised medicine: an envisaged plan which a health provider can implement to a particular patient in order to provide individualized health care in respect of the particular genes.

Medico-legal issues: the legal, ethical parameters and code of conduct concerns which guide practice in the medical profession.

Abstract

The principle of pharmacogenetics and pharmacogenomics (PGx) in health research is not new. However, pursuance thereof has regained momentum in the 21st century. Despite the apparent demand to respond to adverse drug reactions (ADRs), both the national and international medico-legal frameworks have struggled to determine the place of PGx within the scientific and medical arena. It is against such a background that the study sought to explore the medico-legal issues relating to pharmacogenomics and the development of personalised medicine in the context of the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS) in South Africa. The methodology employed in this thesis involves a critical and comparative examination of the international instruments and their monopolistic influences on the multinational pharmaceutical conglomerates (also known as "Big-Pharma") regarding the manufacturing of antiretroviral drugs (ARVs). PGx, which relies on genetic variability, facilitates the development of personalised medicine where adverse drug reactions (ADRs) may be minimised. Currently, PGx in the South African context, and, in respect to people living with HIV, is approached in a fragmented manner. The South African approach to genomic research is caught between the provisions of section 27 of the Constitution's debate concerning the availability of health resources, the protection of individuals and communities, as well as competing human rights issues. Biobanks, necessary for PGx to develop, are increasingly required to store large genetic information for purposes of interpretation and evaluation of ADRs associated with the ARVs. Since genes are personal identifiers, data privacy has started to dominate the international genomic research arena and therefore, invokes added complexities relating to informed consent. Drawing on the English and the Canadian approaches to PGx, the thesis identifies some useful principles and practices for the South African genomic research context. With the need for the implementation of PGx becoming critical, the South African legislator should waste no further time to regulate PGx in a manner to allow the development of personalised medicine so that clinicians are able to make an expeditious clinical decision before the prescription of medication and treatment, most urgently so in the context of HIV and AIDS.

Table of Contents

List of Tables

Chapter 1

Introduction, scope, justification, and methodology of the study

> 'I will prescribe regimen for the good of my patients according to my ability and my judgment and never do harm to anyone. To please no one will I prescribe a deadly drug, nor give advice which may cause his death'.[1] (Hippocratic Oath)

1.1 Background to the study and problem statement

The afore-cited excerpt of the Hippocratic Oath is a modernised version adopted by the Second General Assembly of the World Medical Association (WMA) in Geneva, Switzerland in September 1948, and was last amended by the 68th WMA Assembly in Chicago, United States of America USA) in October 2017. In its original form, the Hippocratic Oath statement itself addresses well-intended medical practice principles in respect of the administration of drugs (medicines). Although drugs and medicine have different effects on the body, the terms, 'drug' and 'medicine' will be used interchangeably for purposes of the current research study, because both terms serve the same purposes of managing disease; as well as dispelling pain and suffering.[2] As a milestone in the treatment of diseases, pharmacology involves the scientific study of drugs and their effects on living systems. The term "pharmacology" bears the root word, "pharma", which is cognate from the Greek term, "pharmakeia", which means "practice of the druggist"[3]. Pharmacology in its full meaning refers to a science studied and practiced in the fields of medicine, biology and drug manufacturing. The science lends itself to on the effects of drugs as well as the movement of drugs or in a human body, animal or plant.[4] The study and provision of medicines and the antecedents support the modern medical treatment endeavours for providing cure, vaccines, prophylaxis, and retardation of the disease progression. However, adverse drug reactions (ADRs) are a reality that accompanies drug administration and its effects and could lead to fatality in some instances.[5]

This research study is contextualized against the backdrop of medico-legal issues relating to pharmacogenomics, in the treatment of the Human Immunodeficiency Virus (HIV) is a global and national matter of concern. The antiretroviral drugs (hereinafter

---

1 See South African Medical Association-Health Market Inquiry May 2019. https://www.wma.net/policies-post/wma-declaration-of-geneva/ accessed 07 December 2022.

2 World Health Assembly A72/17 Provisional Agenda Item 11.7 (4 April 2019) https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_JOUR1-en.pdf accessed 07 December 2022.

3 See Liddell, Scott, Jones' *A Greek–English Lexicon* (commonly known as LSJ). https://lsj.gr/wiki/LSJ:GreekEnglishLexicon accessed 6 October 2022.

4 Anita Wyne, *et al*, *Pharmacotherapeutics for Nurse Practitioner Prescribers* (2nd ed FA Davis Company 2007).

5 JJ Coleman and SK Pontefract, 'Adverse Drug Reactions' (2016) 16(5) Clin Med (Lond) 481-485.

referred to, as ARVs) used in the treatment of HIV are distributed in regiments that are a necessary prescribed medication.

The Centre for Diseases Control (CDC) has referred to HIV (the "mysterious fever"[6]) as an epidemic, whilst the World Health Organisation (WHO) is closely monitoring the number of HIV infections and providing guidelines on the surveillance and clinical stages of HIV.[7] It is estimated that by 2021, the HIV prevalence in South Africa was at 8,2 million people living with HIV. Of these known HIV cases, 270,000 include children infected with HIV.[8]

Globally, 84% of persons living with HIV (PLWH) are currently on antiretroviral treatment (ART), and 66% of PLWH have suppressed viral loads. The treatment of HIV and overall access to health care treatment hinge on standards prescribed by human rights frameworks internationally, such as the International Covenant on Economic, Social and Cultural Rights (ICESCR) treaty.[9] Amongst others, this instrument informed the South African Constitutional Court (ConCourt) when it ordered the South African government's implementation of a plan for ARVs to reduce mother-to-child transmission (PMTCT) of HIV in South Africa.[10]

Despite the availability of treatment for PLWH, other issues associated with human rights that affect the infected worldwide, remain. South Africa was not exempted from litigation when a potential downplaying of human rights of PLWH arose, such as with regard to the patenting of HIV medicine and intellectual property rights (IPR) protection, which affect accessibility, availability, as well as affordability of ARVs.[11] The patenting of HIV medicine was brought to the fore in the South African Constitutional Court (ConCourt) [12], and was defended by the international "Big-Pharma" (that is, the

---

6 CDC, 'Pneumocystis pneumonia—Los Angeles' (MMWR, 1981) https://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm accessed 07 December 2022; 'A Timeline of HIV and AIDS' https://www.hiv.gov/hiv-basics/overview/history/hiv-and-aids-timeline accessed 20 August 2020.

7 Elizabeth Fee and Manon Parry, 'Jonathan Mann, HIV/AIDS, and Human Rights' (2008) 29(1) Journal of Public Health 54–71; http://www.jstor.org/stable/40207166 accessed 16 August 2022.

8 UNAIDS https://www.unaids.org/en/regionscountries/countries/southafrica accessed 16 August 2022.

9 L Stemple, 'Health and human rights in today's fight against HIV/ AIDS' https://doi.org/10.1097/01.aids.0000327443.43785.a1 accessed 6 October 2022.

10 *Minister of Health & Others v Treatment Action Campaign & Others* 2002 (CCT 8/02) 721.

11 P Bond, 'Globalization, pharmaceutical pricing, and South African health policy: managing confrontation with US firms and politicians' (1999) 29(4) International Journal of Health Services 765-792.

12 Amir Attaran & Lee Gillespie-White, 'Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?' (2001) 286(15) Journal of the American Medical Association 1886-1888.

major multinational pharmaceutical companies collectively as a sector of industry).[13] The woe of unfair discrimination of PLWH also plagued the country as was seen in a landmark labour judgment by the ConCourt.[14] Furthermore, South Africa has promulgated legislation to curb any form of discrimination and to uphold the rights of PLWH,[15] including the safeguarding of personal or private information.[16] The trend of curbing discrimination against PLWH was also evident elsewhere in the world, one example of which is the European Court of Human Rights (ECHR) judgment that ruled against the refusal to grant a residence permit based on HIV-positive status. Such refusal is regarded as a form of unjustifiable discrimination.[17]

Compounding the situation of PLWH further, ARVs as mass produced drugs have created many adverse drug reactions (ADRs). Therefore, efforts to address adverse drug reactions need to be studied in the contexts of pharmacogenetics[18] (the branch of pharmacology concerned with the effect of genetic factors on reactions to drugs) and pharmacogenomics[19] (the genetics branch focusing on the way in which an individual's genetic attributes affect the likely response to therapeutic drugs). More recently, the suffix '…omics' has been added to areas of research, rendering 'pharmacogenomics' as a term encompassing all genes in the genome that could determine a body's response to drugs. This branch of genetics is also commonly known as PGx.[20] Since the fields of pharmacogenetics and pharmacogenomics are closely related and overlapping in some respects, this study then frequently refers to pharmacogenomics, which denotes a broader concept relating to all the genes found in the human genome that could determine a person's response to medicines, abbreviated in this regard as PGx. (For purposes of this thesis, pharmacogenetics and pharmacogenomics are referred to as PGx).

---

13 Pat Sidley, 'South African court battle damages drug industry's image' (2001) 322(7287) British Medical Journal 635.

14 *Hoffmann v South African Airways* 2001 (1) SA 1 BCLR 1211.

15 The Promotion of Equality and Prevention of Unfair Discrimination Act 4 of 2000.

16 Protection of Personal Information Act 4 of 2014.

17 *Kiyutin v Russia* 2011 (2700/10).

18 Munir Pirmohamed, 'Pharmacogenetics and pharmacogenomics' (2001) 52(4) *British Journal of Clinical Pharmacolog* 345-347.

19 See - Munir Pirmohamed, 'Pharmacogenetics and pharmacogenomics' (2001) 52(4) *British Journal of Clinical Pharmacology* 345-347.

20 M Subasri, *et al*, 'Pharmacogenomic-Based Personalised Medicine: Multistakeholder Perspectives on Implementational Drivers and Barriers in the Canadian healthcare system' (2021) 14(6) Clinical Transitional Science 2231-2241.

1.1.1 A hierarchical basis for PGx in the promotion of the rights of people living with HIV and AIDS in South Africa

The legal framework relevant for the consideration of the rights of PLWH consists of several international and national legal instruments, discussed in more detail in Chapter 4. At the national level, the apex instrument is the Constitution of the Republic of South Africa, 1996,[21] which entrenches the right to accessing health care services, which resonates with jurisprudence adopted in the African Charter, which stresses that 'the right to access essential medicine for treatment, prevention and palliative care is a necessary condition for leading a healthy and dignified life'. [22] Meanwhile, the 2001 *Resolution of the African Commission on Human and People's Rights on the HIV/AIDS Pandemic* calls on international pharmaceutical companies to render the cost of ARVs affordable and accessible to African people. [23]

Furthermore, Chapter 8 of the National Health Act (NHA) and regulations promulgated in accordance with this chapter, have an indirect bearing on PGx, as it governs the use and control of blood, blood products, gametes and human biological material, including genetic material for medical, research and training purposes.[24] The Medicines and Related Substances Act (MRSA) is also relevant, as it regulates the registration of medicines and associated substances meant for human and animal use.[25] This Act has also influenced the National Strategic Plan for HIV, TB and STIs 2017-2022, which aims to trace the ART success and challenges, amongst others. [26]

The PLWH are entitled to the whole spectrum of rights embodied in the Bill of Rights. One of these rights is of utmost importance as captured in Section 27 of the Constitution; that is, the right of access to health care services, food, water and social security. In his reiteration of the words of Cameron J, Polansky maintains that concerns arising within the realm of the protection of rights revolve around the rights of protection, equality, non-discrimination and social justice.[27] Of necessity, the rights of

---

21 Constitution of The Republic of South Africa, Act No. 108 of 1996.

22 Resolution on Access to Health and Needed Medicines in Africa - ACHPR/Res.141 https://www.globalhealthrights.org/wp-content/uploads/2013/10/Resolution-on-Access-to-Health-and-Needed-Medicines-in-Africa.pdf accessed 07 December 2022.

23 The African Commission on Human and People's Rights, '56 Resolution on the Situation of Human Rights Defenders in Tunisia - ACHPR/Res.56(XXIX)01', 07 May 2001 https://www.achpr.org/sessions/resolutions?id=61 accessed 07 December 2022.

24 See National Health Act 61 of 2003.

25 Medicines and Related Substances Act 101 of 1965 and its Amendment Act 59 of 2002.

26 KL Hopkins, T Doherty and GE Gray, 'Will the current National Strategic Plan enable South Africa to end AIDS, Tuberculosis and Sexually Transmitted Infections by 2022?' (2018) 19(1) SAJHM 796.

27 A Polatinsky, 'Being Judge and Witness: Edwin Cameron's Witness to AIDS' (2008) 35(2) English in Africa 53–70; http://www.jstor.org/stable/40239108 accessed 23 March 2020.

protection of PLWH should include both the right to accessing health care services (which includes ARV access) and drug safety and efficacy detection and monitoring. It is submitted in this study that evidence-based medicine (EBM), whose safety and efficacy have been verified, will further afford PLWH protection against ADRs of ARVs.[28]

The purpose of promoting PGx in the context of the development of ART is that it (PGx) could contribute to improving the quality of care for PLWH, reduce ADRs and in the process, advance the right to health of PLWH in a broad sense. Accordingly, this thesis proceeds from the premise that a failure to apply PGx in the context of HIV treatment for PLWH is an affront to their health rights. Although the Constitution does protect the right to health (which is fundamental to the physical and mental well-being of all individuals), it is understood that the Constitutionally protected right of access to health care services, indirectly promotes the right to health.

1.1.2 Current medico-legal issues in the reasoning behind PGx

The World Health Organisation is also concerned with ADRs and keeps a global database of individual case safety reports on all administered drug or medicine related cases.[29] In the South African case, Section 195(1) of the Constitution provides for basic principles and values for governance in public administration. Following the medico-legal implications relating to ADRs, the South African Health Products Regulatory Authority (SAHPRA) has subsequently been tasked with monitoring the safety of health products in order to contribute to a better understanding of their possible adverse events when they are used outside the controlled conditions of clinical trials. Continuous reporting by health professionals/providers yields important information for the pharmaco-vigilance system in South Africa.[30] To prevent undesirable effects in patients (including PLWH) because of sub-standard health products and inappropriate or unsafe use of health products, an ADR monitoring system was established in South Africa in 1987, coordinated by the regulatory pharmacovigilance unit of SAHPRA. Equally, the South African Medical Association (SAMA) is also supportive of the improvement of the monitoring of clinical outcomes and quality of care.[31] In the

---

28 See D Eddy, 'Evidence-based medicine: a unified approach' (2005) 24(1) Health Affairs 9– 17.

29 WHO Programme for International Drug Monitoring. https://who-umc.org/about-the-who-programme-for-international-drug-monitoring/ accessed 6 October 2022.

30 Communication to Healthcare Professionals May 2021; Reporting of Post-Marketing ADRs 31 January 2020.https://www.sahpra.org.za/wp-content/uploads/2021/06/2.63_ADR__reporting_HCPs_May_2021_v1.pdf accessed 6 October 2022.

31 Grootboom Mzukisi and Sonderup Mark, 'A reflection on the South African Medical Association – past, present and future' 2014 104(6) South African Medical Journal 410-411.

chapters that follow, this thesis further contends that the application of PGx[32] is critically important in the development of ARTs.

A study of ADRs in the context of ARTs is often necessitated by the practice of precision or personalised medicine, which refers to 'an innovative approach to tailoring disease prevention and treatment that considers differences in people's genes, environments, and lifestyles. The goal of precision medicine is to target the right treatments to the right patients at the right time'.[33] With the identification and characterisation of risk factors for ADRs, steps can be taken to minimise medically induced harm. On the other hand, the risk exists that the development of personalised medicine could tamper with a person's rights to dignity, privacy, and confidentiality, because genes are personal identifiers. Protection of personal information becomes compromised should there be a breach of confidentiality or an unwarranted disclosure of the PLWH's personal information.

This thesis also explores and compares the legal contexts of Canada and the United Kingdom in relation to the application of PGx for HIV treatment in order to determine the degree to which these jurisdictions offer valuable lessons from which South Africa could benefit.

Despite the treatment of HIV and AIDS in its 40-year long global prevalence to date, [34] the Sub-Saharan African region remains the mostly infected and affected. South Africa remains highest on the list of those who sero-converts (i.e., develop specific antibodies in the blood serum because of the HIV infection). In South Africa currently, barriers in the treatment of PLWH with ARVs are: access to treatment, affordability, procurement laws, and most importantly, side-effects or non-responsiveness to the drugs. This thesis will also demonstrate that the latter two barriers have impacted negatively on the first two barriers (i.e., access to, and affordability of treatment), and aggravated the control of the HIV pandemic in South Africa.

1.1.3 Potential risks associated with PGx research

As a scientific pursuit, pharmacogenomics could assist in overcoming the side-effects caused by drugs, specifically ADRs. Pharmacogenomics is the combination of pharmaceutical and the patient's genetic composition which interact in an intricate

---

32 K Krebs and L Milani, 'Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good' (2019) 13(39) Hum Genomics..

33 US Food and Drug Administration: Precision Medicine. https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine# accessed 6 October 2022.

34 Chris Beyrer, 'A pandemic anniversary: 40 years of HIV/AIDS' (2021) 397(10290) Lancet 2142-2143; https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01167-3/fulltext accessed 7 October 2022.

manner to produce positive as well as negative drug reactions, which could lead to fatal results for patients.

The impact of supplying patented ARVs to South African PLWH exacerbates the potential of ADRs. This thesis postulates that the application of PGx is critically important in facilitating the development of personalised HIV medication for PLWH. In addition, trade laws such as the TRIPS Agreement,[35] enable the distribution of patented ARVs by pharmaceuticals to curb or retard HIV. However, an unintended consequence has been that this process may impede on the rights of PLWH regarding issues of availability, accessibility, and affordability of the medicine they require for their treatment; not to mention the potential adverse reactions associated with these ARVs. In the latter regard, such impediment is also in conflict with Target 3.8 of the Sustainable Development Goals adopted by the United Nations in 2015, which states that member states are called-to-action to "Achieve universal health coverage including financial risk protection, access to quality essential health care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all" .[36]

The implementation of PGx is made possible through genomic testing through the sequencing of genomes, that is, genotyping of an individual patient. The diverse genetic and genomic composition of South Africans poses a potential barrier for reducing ADRs through PGx in an attempt to develop personalised medicine for PLWH. Biotechnological advancement renders PGx application in this field a reality, yet genetic variants in the population could delay benefits deriving from the application of PGx for PLWH. This is the case, since personalised medicine, enabled through the application of PGx, will require genotyping of a broad range of genetically varied and diverse PLWH on an unprecedented scale. The range of variation is composed of a high admixture found in mixed racial groups and is also affected by genetic factors influenced by the high numbers of asylum seekers and immigrants over a time period.[37] An admixed group is a collective with a mixed genetical ancestry, and varies

---

35 Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organisation, Annex 1C, 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) [hereinafter TRIPS Agreement]; https://www.wto.org/english/docs_e/legal_e/27-trips.pdf accessed 07 December 2022.

36 In Target 3.8, the Sustainable Development Goals (SDGs) refer to 17 development strategies also known as the Global Goals.

37 Louise Warnich, *et al*, 'Pharmacogenomic Research in South Africa: Lesson Learned and Future Opportunities in the Rainbow Nation' (2011) 9(3) Current Pharmacogenomic and Personalized Medicine 191-207.

from the ancestry of homogenous groups, such as the Khoisan, Caucasian, and Indian groups.[38]

The unique deoxyribonucleic acid (DNA) code, which contains the fundamental and distinctive characteristics or qualities of persons, makes people who they are and determines what makes up the thousands of genes in their bodies.[39] DNA also estimates our risk of developing various diseases and determines how our bodies function.

Despite the vast developments made with regard to PGx as a study of how genes respond to drugs, legal developments regarding PGx are limited.

1.2 Rationale for the study

People living with HIV and AIDS are subjected to a range of adverse drug reactions that follow from their prescribed ARVs. Despite the availability of ARVs to PLWH in South Africa, these side-effects could be lethal in some instances, further compromising and impacting on the rights of PLWH in several ways. The high incidence of PLWH on ARVs in South Africa highlights the responsibility of the South African government to mitigate the health risks that ADRs present for PLWH, which, if not addressed, will diminish and reverse earlier legal milestones in securing access to ARVs for people living with HIV in South Africa.

The PGx constitutes an important part of the medicinal therapy, making it possible for patients' DNA to be tested, while also facilitating the recording of the details of the genes that are responsible for metabolising drugs in a patient' s body. When subjected to specially analysed algorithms, these results may create a report that will assist in selecting the appropriate medication suitable for a specific patient's DNA. The PGx relies on the use of DNA as an identifier, which requires coding to match and report findings. In that regard, PGx offers an option through the genotyping of a person's genes to determine compatibility to the specific patient's prescribed medicine. In other words, it makes it possible to move away from the one-size-fits-all approach in prescribed medicine. If applied to the context of prescribed ARVs for PLWH, PGx may completely alter the way ARVs are prescribed in that, specific personalised medical regimes could be developed for specific patient groups; based on their genetic

---

38 SA Tishkoff, *et al*, 'The Genetic Structure and History of Africans and African Americans' (2009) 324(5930) *Science* 1035-1044.

39 Deoxyribonucleic Acid (DNA) Fact Sheet. https://www.genome.gov/about-genomics/fact-sheets/Deoxyribonucleic-Acid-Fact-Sheet. Accessed 22 August 2022

responses to specific ARVs. Since the identity of a patient or group is encrypted out of necessity for purposes of PGx, a robust legal framework for the protection of personal information in the context of the application of PGx for the reduction of ADRs is of the essence.

1.3 Research question

The research problem for this study is informed by previous approaches to the management of HIV in South Africa. The country's approach to HIV during President Mbeki's era was tantamount to a death sentence for PLWH because his approach was focused exclusively on a denial of AIDS statistics, on poverty as a cause of immune deficiency, and on the dangers of antiretrovirals.[40] Despite his government's denial of the correlation between HIV and AIDS, research proved the relationship between HIV and AIDs, which was disregarded at the time.[41] The severity of the disease escalated, and the number of deaths related to HIV intensified before the drugs were finally acquired.[42]

The government's approach at the time was disproportionate to the prioritisation of health care as stipulated in the World Medical Association's Declaration of Seoul on Professional Autonomy and Clinical Independence of 2008, amended in 2018. [43] The declaration refers to the necessity of priority setting, funding decision making and resource allocation/ limitations processes that need to be transparent. Reference is also made to the essential priorities in health care and alludes to economic impediments that may influence clinical autonomy by imposing, for example, pricing that is inconsistent with the best interest of patients. The hegemony of the "Big-Pharma" is apparent in the laws, policies and strategies emanating from high-income-countries, strengthened by international instruments and bodies and instruments such as the World Trade Organisation (WTO) and other trade related agreements, [44] seek to protect the patents of IP rights holders.

---

40 D Fassin and H Schneider, 'The politics of AIDS in South Africa: beyond the Controversies' (2003) 326(7387) British Medical Journal 495-497.

41 PH Duesberg, 'Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome: Correlation but not Causation' (1989) 86(3) Proceedings of the National Academy of Sciences U S A 755-764.

42 Pat Sidley, 'HIV/AIDS Responsible for 25% of Deaths in South Africa, Report says' (2001) 323(7318) British Medical Journal 890.

43 Adopted by the 59th WMA General Assembly, Seoul, Korea, October 2008 And amended by the 69th WMA General Assembly, Reykjavik, Iceland, October 2018; https://www.wma.net/policies-post/wma-declaration-of-seoul-on-professional-autonomy-and-clinical-independence/ accessed 8 October 2022.

44 WTO agreements are the result of the 1986–94 Uruguay Round negotiations, signed at the Marrakesh ministerial meeting in April 1994. There are about 60 agreements and decisions totalling 550 pages.

The mass production and a one-size-fits-all approach of ARVs is less concerned with the genetic profiles of individuals or groups than with profitability and protection of intellectual property rights. These mass-produced ARVs are the cause of ADRs experienced by people living with HIV.

This thesis postulates that the adverse drug reactions associated with patented ARVs infringes on the rights of PLWH, in addition to posing serious health and safety risks and negative side-effects. The thesis asserts further that an adoption of PGx in the context of the development of ARVs for PLWH will contribute in alleviating this burden in respect of the development of personalised medicines for PLWH, as well as promoting the rights of PLWH. Such an approach to personalised medicine will best give effect to the rights of PLWH to safe and effective medication, thus prolonging the quality of their lives in a manner that supports their rights to human dignity, equality, and access to health care services, including the access to effective and safe medication. Realising this objective requires a robust legal framework that guides PGx research in a safe and responsible manner, sensitive to the ethical, legal, and social considerations that apply to the PLWH.

1.4 Aims and objectives of the study

The aims and objectives of this study are inextricably linked to the research question above.[45] Firstly, the thesis will explore the discrepancy created by the TRIPS Agreement and the supply of ARVs to PLWH in South Africa, including the effects of this Agreement on PLWH's access to ARVs, including the incidence of ADRs. Secondly, the thesis explores the application of PGx in the context of ARV development to determine its impact on the efficacy and safety of ARVs in an attempt to determine whether it may facilitate the development of personalised ARV medicines.

The examination of the two issues above will also include a comparative overview of how the legal framework of Canada and the United Kingdom addresses these issues. The rationale for the selection of these two jurisdictions follows from Section 39 of the Constitution which provides that:

> "[W]hen interpreting the Bill of Rights, a court, tribunal or forum (a) must promote the values that underlie an open and democratic society based on human dignity, equality and freedom; (b) must consider international law; and (c) may consider foreign law".[46]

---

45 Uldrich Flick, *Introducing Research Methodology*, (3rd Edn Sage 2020).

46 Constitution of the Republic of South Africa, Act 108 of 16.

The thesis will also highlight the relevant fundamental rights at stake for PLWH in the context of their right to access health care services, considering resource availability as a built-in limitation to the right to access health care services in terms of Section 27 of the Constitution.

In the final instance, the thesis will make recommendations for the improvement of the existing legal framework governing the access of PLWH to safe and effective ARVs in the form of personalised medicine. The afore-cited aims will require a discussion of specific issues, namely:

1. the ARV procurement process of the National Department of Health and its impact on the supply of ARVs in South Africa, including the accessibility, affordability, safety and efficacy of these ARVs to PLWH;
2. the impact of HIV in the current South African context;
3. the link between the procurement of ARVs and the fulfilment of the right of access to health care services for PLWH;
4. the role of PGx in the manufacturing of ARVs in order to limit ADRs;
5. the extent to which genetic research is governed in the present South African legal framework, and whether this legal framework covers the application of PGx in manufacturing personalised medicine in the form of ARVs; and
6. the need for protecting confidentiality and privacy in genetic and genomic research in South Africa.

1.5 Research design

This study involves a desktop-based, literature review and medical and legal enquiry which is an anticipatory antecedent existing alongside medical practice.[47] The study will also follow a rights-based approach, as the right to quality health care "is an accumulation of constitutional rights", for example, right to life and dignity.[48]

This thesis argues that necessary and appropriate regulatory form in health legislation has traditionally been slow, unfortunately. However, it is hoped that the thesis will demonstrate the importance of PGx in improving the health of PLWH in South Africa, particularly regarding the elimination of ADRs.[49]

---

47 CJ Albertyn, 'Medico-legal problems in general practice' (1934) 8(6) SAMJ 199.

48 Pieter Carstens and Debbie Pearmain, F*oundational principles of South African medical law* 2007 (LexisNexis 2007).

49 B Tata, A Ambele, and S Pepper, 'Barriers to Implementing Clinical Pharmacogenetics Testing in Sub-Saharan Africa' (2020) 12(9) A Critical Review Pharmaceutics 809.

1.6 Study methodology

The study has adopted a desktop, literature-based methodology, involving the consultation of relevant national laws, policies, regulations, guidelines and strategies, scholarly books, the internet, legal journal articles and other relevant texts. Where relevant, reference will be made to certain medical and clinical concepts, specifically with regard to HIV, AIDS, and PGx. Relevant case law, local and foreign laws, will be analysed, as well as appropriate international legal instruments that have a bearing on the topic, in an attempt to seek solutions for the national context, as well as identify regulatory gaps that may exist.

1.7 Anticipated outcomes of the study

The study will demonstrate the negative effects of the TRIPS Agreement on the procurement of patented ARVs for PLWH in South Africa, particularly regarding issues of efficacy and safety of the ARVs. The study also proposes that the application of PGx in the context of ARV development will play a significant role in addressing the prevailing adverse reactions to ARVs, and if adopted for South African PLWH, that it may improve the health of PLWH and enhance their fundamental rights.

To understand the study's potential outcome, it is worth noting that the ARVs initially supplied to South Africa were mainly manufactured by international pharmaceutical companies in terms of trade agreements between the National Department of Health and certain international pharmaceutical companies. The efficacy and safety of these drugs were not conducted on South African patients, which was the case in many lower income countries at the time when ARVs were rolled out (late 1990s and early 2000s).[50] The emergence of PGx in the development of safe and personalised medicines holds specific benefits for PLWH who take prescribed ARVs that have serious adverse drug reactions.

The integration of PGx into medical settings is often regarded as a chicken-or-the-egg proposition. On the one hand, healthcare professionals need evidence that genomics improves doctors' ability to diagnose and treat disease, but genomics should first be implemented into medical settings to gather that evidence.[51] A genomic test can give a range of information about the individual's identity and how the individual's body

---

50 Anthony Butler, South Africa's HIV/AIDS policy, 1994-2004: How can it be explained? African Affairs, Volume 104, Issue 417, October 2005, Pages 591-614, https://doi.org/10.1093/afraf/adi036. accessed 09 June 2023.

51 Steven Benowitz, 'Looking across genomic medicine's gaps and opportunities' (06 July 2016) https://www.genome.gov/news/news-release/GM8-Looking-across-genomic-medicines-gaps-and-opportunities accessed 21 August 2022.

metabolises drugs. The results of the test will indicate which medication would be best for an individual patient, as well as what dosage of medication would provide the optimal effect and minimal side-effects. This information will make the difference between effortless medical treatment and one with severe or even fatal adverse effects.

1.8 Outline of the thesis

Chapter 1 of the thesis outlines the problem statement, rationale for the study, as well as the research question and methodology adopted in the thesis.

Chapter 2 provides a historical overview of the clinical manifestation of HIV and the role of ARVs in the treatment of the virus. Based on the fact that the virus generates a reverse transcription in the viral RNA genome into DNA, the reversal of the genetic formation varies in the affected cells, and the contrasts are realised from person to person.[52] Therefore, pharmacovigilance on the ARVs facilitates and reveals the varied genetic information and extends the scope of individual response to the ART or ARVs.[53] This chapter explores the nexus between pharmacology and PGx, followed by a discussion of the link between HIV treatment and PGx. A systematised review of published literature, which explores the way HIV as a viral disease enters an individual's genetic cells, known as T-Cells, is provided.[54] This background is necessary for the investigation of the role of ART, which presents an avenue for delaying the progression of the virus, and how genes may signal a pathway and guide the development of therapy for PLWH. The genetic mutations in HIV that increase an individual's CD-4 count presents risk to HIV patients if the detection is not implemented timeously.[55]

Chapter 3 focuses on the adverse consequences relating to the protection of intellectual property rights in the manufacturing of ARVs following the HIV pandemic. The chapter discusses the socio-economic and legal dimensions of patents and IPR and its impact on the manufacturing of ARVs. The progression of HIV into a pandemic catapulted the NIAID (National Institute of Allergy and Infectious Diseases, one of the 27 institutes and centres that constitute the National Institutes of Health (NIH) of the

---

52 Lucky Mulwa and Marc Stadler, 'Antiviral Compounds from Myxobacteria' (2018) 6(3) Microorganisms 73.

53 YD Mahnke*, et al*, 'Reconstitution of Peripheral T Cells by Tissue-Derived CCR4+ Central Memory Cells Following HIV-1 Antiretroviral Therapy' (2016) 1(2) Pathog Immun 260–290.

54 D Vignali, L Collison, and C Workman, 'How Regulatory T Cells Work' (2008) 8(7) Nature Review Immunol 523–532; https://doi.org/10.1038/nri2343 accessed 14 October 2021.

55 Redmond Smyth, Miles Davenport and Johnson Mak 'The Origin of Genetic Diversity in HIV-1' (2012) 169(2) Virus Research 415-429.

United States Department of Health and Human Services (HHS)) into playing a significant role in unravelling the complex position of ART for PLWH.[56] Some of these complexities include the issue as to who will be accorded the patent for the drugs, as well as who will be responsible for monitoring the protection of the intellectual property IP in the patented medicines.[57] The IP system requires the involvement of international bodies as well as the geo-political entities to accept the trade prescripts. This chapter will also explore how the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) influences health related issues, especially the protection of ARV patents. This field is dominated by patents held by high-income countries (HICs), which has facilitated the one-size-fit-all approach for the manufacturing of ARVs, thereby limiting and eroding the rights of PLWH in low and middle-income countries (LMICs). The chapter further investigates the role of the National Drug Policy in South Africa, including the relevant provisions of the Medicines and Related Substances Act and its regulations.[58]

Chapter 4 explores the South African legal framework relating to HIV treatment and the development of personalised medicine. This chapter considers the existing legal framework relevant to the application of PGx for PLWH in an effort to reduce or limit ADRs. This chapter also explores relevant medico-legal aspects related to genetic and genomic research, including PGx; as well as pertinent legal, ethical and social issues. Comparative legal perspectives regarding the monitoring of HIV provides an analysis of the medico-legal systems utilised in Canada and the United Kingdom in the management of ADRs. This is particularly significant, as such comparison will place our current local framework into perspective and substantiate on the gaps that exist. The right to access health care services, the right to human dignity, equality, privacy, and the right to life of PLWH are at the core of the rights afforded to PLWH.[59] This chapter asserts that the lack of recognition of the potential effects of ADRs is not mitigated by the surveillance of ADRs through pharmacovigilance after the administration of ARVs to PLWH.[60]

---

56 P Piot, S Russell, and H Larson, 'Good Politics, Bad Politics: The Experience of AIDS' (2007) 97(11) American Journal of Public Health 1934-1936.

57 http://www.unitaid.org/assets/ARV_Snapshot_April2014.pdf accessed 25 October 2020.

58 Medicines and Related Substance Act 101 of 1965.

59 E Reed, et al, 'Confidentiality, Privacy, and Respect: Experiences of Female Sex Workers Participating in HIV Research in Andhra Pradesh, India' (2014) 9(1) Journal of Empirical Research on Human Research Ethics 19-28.

60 The first thalidomide-affected baby was born in Germany on 25 December 1956 to a Chemie Grunenthal employee. https://www.thalidomidetrust.org/about-us/about-thalidomide/ accessed 03 September 2019.

Chapter 5 highlights the potential for personalised medicines, as well as their effect on the alleviation of ADRs in PLWH. The genotyping of PLWH requires a consideration of fundamental rights issues, specifically those relating to confidentiality, privacy and informed consent. This chapter further explores the problematic tension between ownership of personal and familial genetic information on the one hand, and 'societal' ownership in genetic material (e.g., the notion of genetic sovereignty) on the other. Individual patients' genetic, physiology and pathology are intrinsic factors that play a role in the specific patient responses to ARVs. Moreover, the latter is also compounded by the absorption, distribution, metabolism, and elimination (ADME) of the drugs in each instance.[61] Further extrinsic factors, such as age, weight, diet and the environment that could also influence ADRs in an individual.[62]

Chapter 6 focuses on PGx research and its impact on the protection of personal information of PLWH. The application of PGx requires the dissection of patients' genes and genotype in an attempt to match individual genes to the most suitable medicine. This research requires the processing of highly personal patient information which could be stored in databases for future reference. The burden of protecting personal information will depend on the place of treatment, manufacturers and administrators of the medication. The interdependence of passing the patient information between different data points for the purpose of PGx requires not only on assurances regarding data integrity, but also on the protection of the patient's rights to dignity, privacy and confidentiality.[63] The role of the Protection of Personal Information Act[64] is of critical importance in the South African context. Accordingly, the chapter briefly explores the comparative legal frameworks relating to the protection of personal information in the United Kingdom and Canada. This comparative exposition of legislation, policies and court interpretations in the jurisdictions provide and expose the disparities that exist in the protection of personal information. (With the liabilities created by HITECH modifications to HIPAA (Health Insurance Portability and Accountability Act of 1996) several years ago in the United States, the General Data Protection Regulation (GDPR) in the European Union and updates to the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada, as well as changes across the

---

61 Muead Jamal Alomar, 'Factors affecting the development of adverse drug reactions (Review article)' 2014) 22(2) Saudi Pharm J 83-94.

62 Alex Diaz-Papkovich, *et al,* 'UMAP reveals cryptic population structure and phenotype heterogeneity in large genomic cohorts' 01 November 2019. https://doi.org/10.1371/journal.pgen.1008432 accessed 14 October 2021.

63 S Helbig and LB Harman, *Ethical Challenges in the Management of Health Information 2nd ed* (Jones Bartlett Publishers 2006) 611.

64 Protection of Personal Information Act 13 of 2013.

globe to other regulations, there are now mandatory investigation and fines, data breach notification, and significantly increased enforcement). [65]

Chapter 7 presents the summary of the findings from each of the preceding chapters, as well as the recommendations aimed at improving the *status quo* (i.e., current practices in the field of PGx). This chapter will provide guidance on how to introduce PGx into the existing legal framework governing genetic research. The development of personalised medicine in the field of HIV treatment should be regarded as a critical need, not only to address the incidence of ARVs, but to promote the health of PLWH and to give better effect to the protection of their fundamental rights relating to life, human dignity, equality, and privacy. Notwithstanding South Africa's LIC status, the thesis argues that the government has a Constitutional responsibility to alleviate the health risks encountered by people living with HIV.

1.9 Conclusion

This chapter has provided the context for this study. It has also posited PGx as a measure through which the rights of PLWH may be enhanced and ADRs be alleviated. It is hoped that this study will assist in illuminating the benefits that PGx hold for PLWH in South Africa.

The next chapter explores the clinical manifestation of HIV and introduce PGx for the development of personalised medicine in the treatment of HIV.

[65] https://naidonline.org/programs/doctors-office-marketing/ accessed 20 April 2020.

Chapter 2

Clinical manifestation of the human immuno-deficiency virus (HIV)

2.1 Introduction

Since HIV is a blood-borne disease, there occurs a contamination in the blood's white cells which is characterised by high levels of the virus CD-count in the infected patient. The infection is initially established in the blood, which explains the reason for the virus to be transmitted by mothers and infects their unborn *in utero*.[66] HIV survives by expediting its replication rate and increases inflammation and tissue destruction in the infected body until the person shows the signs and symptoms of AIDS.[67]

The prevalence of AIDS occurs when conditions are favourable to the virus because the immune system is weakened due to HIV infection. Currently, HIV and AIDS are among the most globally recognised public health threatening pandemics.[68] The PLWH are at a much greater risk of developing opportunistic diseases such as active Tuberculosis (TB) once infected, which increases as the degree of immune suppression increases.[69] This means that PLWH may be subjected to a multiplicity of treatment regimes.

As the virus unfolds and develops, and is treated, persons living with HIV may develop ADRs (adverse drug reactions) to the antiretrovirals (ARVs) with which they are treated. This chapter will focus, among others, on the reasons underpinning the use of ARVs, and how the incidence of ADRs has turned the focus to PGx and the development of personalised medicines in the context of HIV.

The first reason relates to the status of HIV as a public health threat, especially in South Africa, which is one of the countries with the highest HIV burden.[70] As scientists strive to find a cure for HIV, current research on HIV consists of clinical trials and a review of literature in search of a vaccine; and also, finding an ultimate cure for HIV. Research and development have produced more than 20 dual and triple combined ARV medications or combination regimens.[71] Safe and effective treatment for HIV is

---

66 https://www.who.int/health-topics/hiv-aids#tab=tab_1 accessed 17 August 2022.

67 V Simon, D Ho, and A Karim, 'HIV/AIDS Epidemiology, Pathogenesis, Prevention, and Treatment' (2006) 368(9534) Lancet 489-504.

68 P Piot and TC Quinn, 'Response to the AIDS Pandemic--a Global Health Model' (2013) 368(23) New England Journal of Medicine 2210-2218.

69 https://hivinfo.nih.gov/understanding-hiv/fact-sheets/what-opportunistic-infection accessed 17 August 2022.

70 https://worldpopulationreview.com/country-rankings/hiv-rates-by-country accessed 18 October 2022.

71 Vitoria, *et at*, 'Current and Future Priorities for the Development of Optimal HIV Drugs' (2019) 14(2) Current Opinion in HIV and AIDS 143-149.

impossible without understanding how the developed drugs are assimilated and metabolised in the body of the HIV infected person.

Antiretrovirals are manufactured by different pharmaceutical companies whose medicine are protected by patents, which, in turn, are intended to keep the companies afloat. This partly explains the competitive drug pricing which impacts on affordability, accessibility, and availability of the ARVs. People living with HIV are often listed as potential research participants, whose participation in clinical trials over the years has contributed significantly to the current treatment regime for HIV and AIDS.

However, despite a range of available antiretroviral treatment approved both locally and internationally for the treatment of HIV, there is no conformity in responses to the drugs in the bodies of those infected with the virus. Relying on a combination of drugs in the treatment of HIV has become a common practice, as different drug combinations in some instances are necessary to enhance the efficacy of treatment. However, the selection of the optimal combination and the optimal doses remain largely a matter of 'trial and error'.[72] The concomitant adverse drug reactions associated with the ARV treatment cannot be ignored or underestimated. The procurement of some of the drugs and/ or compounds relies on a broad range of different international manufacturers, leading to concerns regarding the safety and efficacy of the different ARVs. It is possible for a human body to develop resistance and identifiable adverse reactions to some drugs; for example, hypersensitivity (side- effects) and other toxic drug effects.[73] The complexities of ARTs and highly active antiretroviral therapy, (HAART),[74] discussed in this chapter with reference to pharmacodynamics and pharmacokinetics, may be explained by reference to the so-called individualistic 'transduction pathways' in the receptor cells of patients to allow the effect of drugs.[75] This relates to intracellular receptors to drugs, which bind their ligand inside of the cell and directly activates the response of the genes to the drug.

Thus, this chapter seeks to outline and to provide an overview of the manifestation of HIV and the role and function of the science of PGx in relation to HIV treatment.

---

72 PN Bennett and MJ Brown, *Clinical Pharmacology 9th ed* (McGraw-Hill Medical 2003)135; Richard Murphy, *et al,* 'Co-administration of Lopinavir/Ritonavir and Rifampicin in HIV and Tuberculosis Co-Infected Adults in South Africa' (2012) 7(9) Public Library of Science.

73 http://www.aidsmap.com/Monitoring-the-safety-and-effectiveness-of-HIV-treatment/page/2841924/ accessed 16 October 2018.

74 HAART is a term coined in the late 1990s to describe the effectiveness of combination drug therapies used to treat HIV.

75 Daniel Jonker, *et al*, 'Towards a Mechanism-Based Analysis of Pharmacodynamic Drug–Drug Interactions in Vivo' (2005) 106 Pharmacology & Therapeutics1-18.

Accordingly, the chapter further aims to demonstrate, among others, that the notion of one-size-fit-all manufacturing of medicines does not offer the expected safety, quality and efficacy in the manufacturing of drugs and medicines for treating HIV. Therefore, in achieving the afore-cited objectives of this chapter, the following factors were considered:

1. the clinical aspects of HIV;
2. the origin and pharmacology of the ARVs in relation to HIV and their role in the treatment of HIV;
3. limitations in the treatment of HIV infection and the ADRs;
4. the safety and efficacy of the ARVs on South African patients not genotyped for a specific regimen; and
5. the role of PGx in addressing the prevailing adverse reactions to ARV drugs.

2.2 The clinical manifestation of HIV

The term, "manifestation" alludes to the different forms of HIV that are presented in PLWH and provides an overview of the different treatment regimens prescribed for the relevant strains. Currently, there are two principal strains of HIV recognised by researchers, namely, HIV 1 and HIV 2, [76] both of which have important genetic differences in their substrate and inhibitor binding enzymes. Additionally, HIV-2 has a different structural level and generally progresses more slowly, leading to lower viral load and slower risk of becoming a disease. Thus, this thesis focuses on HIV-1. There is a common belief that HIV-1 is the first strain discovered, which is the strain that gave rise to the worldwide pandemic [77]

Historically, the advent of the AIDS pandemic was made public on 5 June 1981, when the U.S. Centers for Disease Control and Prevention (CDC) published a Morbidity and Mortality Weekly Report (MMWR) describing cases of a rare lung infection known as *pneumocystis carinii pneumonia* (PCP) in five young, previously healthy gay men in Los Angeles. That edition of the MMWR marked the first official reporting of what has become known as the AIDS epidemic.[78]

---

[76] MR Smallman-Raynor and AD Cliff, 'Civil war and the spread of AIDS in Central Africa' (2009) 107 Cambridge University Press 69-80.

[77] S Lovgren, 'HIV originated with monkeys, not chimps, study finds' (National Geographic Science News, 12 June 2003) https://www.nationalgeographic.com/science/article/news-hiv-aids-monkeys-chimps-origin accessed 17 September 2021.

[78] CDC, 'Pneumocystis Pneumonia - Los Angeles' (MMWR 03 March 1999) https://www.cdc.gov/mmwr/preview/mmwrhtml/lmrk077.htm accessed 21 October 2018.

The pathophysiology of HIV is that it is a chronic blood-borne disease, which belongs to a family of viruses. The latter can create their own DNA and reproduce copies of their RNA (Ribonucleic acid) genome. Thus, the RNA reverses the flow of genetic information. [79] As stated in the introduction above, HIV - a blood-embodied disease - is embedded in the DNA molecule that contains the instructions that a human body requires for the development and reproduction of cells. Furthermore, HIV spreads mainly through parenteral (not involving the intestines or the digestive tract), anal or vaginal sex or by sharing drug-use equipment with an infected person.

The transmission of HIV can also occur by contact with infected blood or from mother to child during pregnancy, childbirth or breast-feeding.[80] Furthermore, HIV attacks the body's immune system by derailing the ability of the white cells' cytotoxic T-Cells[81] to defend the body [82] The CD4 T cells play a central role in immune protection through their capacity to help B cells make antibodies, to induce macrophages to develop enhanced microbicidal activity, to recruit neutrophils, eosinophils and basophils to sites of infection and inflammation; and to orchestrate the full panoply of immune responses through their production of cytokines and chemokines. The human body then succumbs to this invasion, which eventually leads to death.

The human body consists of millions of blood cells, of which about 1% are white cells that protect the body against infections.[83] A type of white cells, better known as T-helpers, play an important role, as these are the cells that are attacked by the HI virus, a process which damages the body's ability to fight against infection.[84] The white blood cells are responsible for organising and arousing (activating) the immune system's other cells to produce antibodies against an invader, or to attack a foreign cell directly.[85] It could take years for the human body' weakened state to manifest.

---

79 https://www.livescience.com/37247-dna.html accessed 17 October 2018.

80 https://www.mayoclinic.org/diseases-conditions/hiv-aids/symptoms-causes/syc-20373524 accessed 22 October 2018.

81 J Zhu and E William, 'CD4 T cells: Fates, Functions, and Faults' (Science Direct 01 September 2008) https://doi.org/10.1182/blood-2008-05-078154 accessed 21 September 2018.

82 Low CD-4 count levels occur when a higher rate of virologic failure has been observed in those with low pre-treatment, drug resistant and defaulter HIV patients. Antiretroviral regimen is a consideration as an initial or some cases an alternative therapy based on specific clinical scenarios. https://aidsinfo.nih.gov/guidelines accessed on 13 September 2018.

83 During an infection, the blood delivers more immune cells (white cells) to the site of infection, where they accumulate to ward off harmful invaders. https://www.ncbi.nlm.nih.gov/books/NBK2263/ accessed 22 October 2018.

84 HIV is a virus that spreads through certain body fluids that attack the body's immune system, specifically the CD4+T cells, often called T cells. https://www.cdc.gov/mmwr/preview/mmwrhtml/lmrk077.htm accessed 23 July 2018.

85 Aimee Ansari and Joseph Etzel, 'Immune-Based Therapies for the Management of HIV Infection: Highly Active Antiretroviral Therapy and Beyond' (Journal of Pharmacy Practice 01 December 2000) https://www.doi.org/10.1106/U537-L0GG-CD0J-QN0Q accessed 24 July 2018.

Therefore, it is not easy to identify an HIV infected body without testing an individual for HIV.

Since the virus is detected through blood tests, serological tests, such as enzyme immunoassays (EIAs)[86] (used to detect the presence or absence of antibodies to HIV-1 and/ or HIV p24 antigen[87]) it is worth mentioning that HIV testing should be made a routine test, notwithstanding that such testing is instrumental and an essential gateway to HIV prevention, treatment, care, and support services.[88]

The AIDS stage denotes the phase at which the body is no longer able to guard against infection and disease and at which point external assistance is necessary to boost the CD-4 count of a PLWH. This stage is better known as Stage Three HIV.[89] During this stage, infected persons may develop collective opportunistic infections, such as pneumonia or tuberculosis as a result of their immune system's inability to defend itself. The pathology of HIV indicates that HIV is an intracellular organism, which uses the host cell's genetic material for its own replication.[90] This explains the role of genetics and genomics regarding research towards development and manufacturing of the ARV drugs.

Genetics is a science that reflects on the pattern of variations in a person's genetic inheritance. Genomics, on the other hand, encapsulates the complete set of human DNA,[91] which includes all of the human genes structure. Each genome contains all the information needed to build and maintain the whole of the human being. In humans, a copy of the entire genome is more than 3 (three) billion DNA base pairs is contained in all cells that have a nucleus.

2.3 HIV and AIDS in South Africa: brief overview

According to population estimates for 2021, the overall HIV prevalence rate in South Africa was approximately 13.7% of the total population.[92] In the same year, the number

---

86 Early diagnosis and rapid initiation of treatment remain a key strategy in the control of HIV.

87 http://www.who.int/news-room/fact-sheets/detail/hiv-aids accessed 10 October 2018.

88 https://www.hiv.gov/federal-response/pepfar-global-aids/pepfar accessed 27 September 2018.

89 Arora D R, Maheshwari M and Arora B, 'Rapid Point-of-Care Testing for Detection of HIV and Clinical Monitoring' (ISRN AIDS, 23 May 2013) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767371/ accessed 22 October 2018.

90 Gustav Schellack, *Pharmacology in Clinical Practice - Application Made Easy for Nurses and Allied Health Professionals 2nd ed* (Juta 2010) 188.

91 Ryan Wenger, et al, *Core Curriculum for Primary Care Pediatric Nurse Practitioners* (Mosby 2006) 154.

92 Department of Statistics South Africa, 'Statistical Release P0302: Mid-year Population Estimates (19 July 2021) https://www.statssa.gov.za/publications/P0302/P03022021.pdf accessed 07 December 2022.

of people living with HIV in South Africa was estimated at 8,2 million.[93] For adults between the ages of 15 and 49 years, an estimated 18.9%of the population was HIV positive.[94]

According to South Africa's report on the 2015 Millennium Development Goals with regard to HIV detection and treatment, the mode of testing for HIV is still based on an opt-in model (meaning that testing is done on a voluntary basis), which raises concerns as to the actual facts. The persistently higher risk and HIV prevalence rates among young women are associated with, inter alia, social and behavioural factors such as age-disparate relationships. Other risk factors of HIV acquisition among young women include early sexual debuts and perceptions concerning multiple sexual partnerships.

The erstwhile President of South Africa, President Mbeki and the Minister of Health at the time, Dr Manto-Shabalala, were concerned about the link between HIV and AIDS. Since the available drugs AZT and Nevirapine were not tested on South African patients, the issue of drug safety and efficacy was a major concern for the former President.[95] President Mbeki started to advocate the view that poverty and poor diet are linked to HIV.[96] Whilst the debate around ARTs and diet ensued, millions of people were losing their lives through AIDS.[97] The Treatment Access Campaign (TAC) rejected these views and called for an immediate release of the drugs.[98]

[99] In 2012, South Africa had more PLWH, estimated at 6.4 million, than any other country worldwide. South Africa achieved four of eight MDG indicators, including HIV prevalence among those aged 15–24 years. South Africa experienced an increase in the number of HIV infections during the 1990s and early 2000s, which coincides with the era of President Mbeki's leadership that was characterised by confusion and

---

93 http://www.unaids.org accessed 13 March 2019.

94 http://www.statssa.gov.za accessed 13 March 2019.

95 Anthony Brink, *Poisoning our children: AZT and Nevirapine in Pregnancy* (Open Books 2005). See http://www.tig.org.za/pdf-files/affidavit-aug06/4%20Poisoning%20our%20Children.pdf access 15 September 2021.

96 Nono Simelela, *et al*, 'A Political and Social History of HIV in South Africa' (2015) 12(1) Curr HIV/AIDS Rep 256–261.

97 Adele Baleta, 'South Africa to redouble efforts to control the spread of HIV' (04 September 1999) https://doi.org/10.1016/S0140-6736(99)80032-4 accessed 14 October 2021.

98 Michael H Merson, et al, 'The history and challenge of HIV prevention Author links open overlay panel' (2008) 372(9637) Lancet 475-488.

99 See https://www.un.org/millenniumgoals/2015_MDG_Report/pdf/MDG%202015%20rev%20(July%201).pdf accessed 15 September 2021.

denialism regarding the causes and correlation of HIV and AIDS.[100] On 28 October 1999, President Mbeki made the following statement in Parliament:

> [T]here ... exists a large volume of scientific literature alleging that, among other things, the toxicity of this drug [AZT] is such that it is in fact a danger to health. These are matters of great concern to the Government as it would be irresponsible for us not to heed the dire warnings which medical researchers have been making. I have therefore asked the Minister of Health ... to go into all these matters so that ... we ourselves, including our country's medical authorities, are certain of where the truth lies.[101]

A further complication was that the path from research to market -even for successful candidates -has become long, costly and inefficient. While these debates went on, many people living with HIV and AIDS continued to suffer because of the then government's approach to HIV and AIDS programmes. The government's laxity resulted in an increase in HIV infections. More than 330,000 lives or approximately 2.2 million person-years were lost because a feasible and timely ART programme was not implemented in South Africa. Thirty-five thousand babies were born with HIV, resulting in 1.6 million person-years lost by not implementing a PMTCT programme using Nevirapine.[102] Scientists, including the Zimbabwean physician, Pride Chigwedere, blamed President Thabo Mbeki for his "attitudes" which resulted in the early death of thousands of people in South Africa.[103]

Together with the PLWH, the scientific community also felt voiceless and frustrated as their research was questioned and criticised by the government and politicians. It is for this reason that the scientific community laid the blame for the crisis regarding the delay in rolling out the HIV and AIDS treatment programmes on the government and former leaders at the time.[104] The most affected by the delay in rolling out the HIV/AIDS programme were undoubtedly rural and disadvantage communities.

Unfortunately, the politicians, policy makers, community leaders and academics who directly or indirectly supported the Mbeki government's handling of the HIV issue, denied what was patently obvious, namely that the epidemic of HIV and AIDS would affect not only the health of individuals, but also the welfare and well-being of households, communities and in the end, entire societies. This approach contradicted

---

100 Tony Karon, 'Why South Africa Questions the Link Between HIV and AIDS' (Time, 21 April 2000) http://content.time.com/time/arts/article/0,8599,43510,00.html accessed 19 September 2018.

101 Anthony Brink, *Poisoning our children: AZT and Nevirapine in pregnancy* (Open Books 2005).

102 P Chigwedere, *et al* 'Estimating the Lost Benefits of Antiretroviral Drug Use in South Africa' (2008) 49(4) Journal of Acquired Immune Deficiency Syndromes 410-415.

103 https://scimedskeptic.wordpress.com/tag/vaccination/ accessed 22 October 2018.

104 TAC is a South African HIV/AIDS activist organisation which was co-founded by the HIV-positive activist Zackie Achmat. https://www.tac.org.za/category/about accessed 22 October 2018.

Section 195(1)(e) of the Constitution, which entrenches the value of a positive response by the government to the public's needs.[105]

2.4 The WHO's response to HIV and AIDS

In 2015, the 69th World Health Assembly endorsed the new Global Health Sector Strategy on HIV (2016-2021).[106] The strategy includes five strategic directions that would guide priority actions by countries and by WHO over the six years. The strategy encompasses "…a vision, goals, targets, guiding principles and priority actions for ending the sexually transmitted infections epidemic as a public health problem."[107] The strategic directions of this strategy are as follows:

- information for focused action (know your epidemic and response);
- interventions for impact (covering the range of services needed); and
- financing for sustainability (covering the costs of services) and innovation for acceleration (looking towards the future) [108].

The WHO is a co-sponsor of the UNAIDS, and leads activities on HIV treatment and care, HIV and Tuberculosis co-infection, and jointly coordinates the work on the elimination and prevention of mother to child transmission (PMTCT) of HIV with the UNICEF.

The WHO first published guidelines on the use of ART for HIV infection among adolescents and adults in 2002, and on ARV drug use to prevent MTCT in 2004. The updated guidelines of 2006 introduced the concept of a public health approach, with simplified and harmonised ART regimens. In 2013, the WHO revised and combined these and other ARV-related guidance documents into consolidated guidelines that address the use of ARV drugs for HIV treatment and prevention across all age groups and populations, based on the HIV service continuum. In 2016, the guidelines were again updated and published.[109]

---

105 Constitution of the Republic of South Africa, 1996.

106 'The Sixty-ninth session of the World Health Assembly' (World Health Organisation, 16 May 2016) http://www.who.int/governance/en/. accessed 20 September 2018.

107 http://www.who.int/reproductivehealth/ghs-strategies/en/ accessed 20 September 2018.

108 Global health sector strategy on HIV 2016-2021, this is part of an ambitious target of the 2030 Agenda for Sustainable Development.

109 World Health Organisation, 'Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach 2nd ed' (World Health Organisation 2016) http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1 accessed 15 September 2021.

The 2016 guidelines introduced new recommendations, including the recommendation to provide lifelong ART to all children, adolescents, and adults, including all pregnant and breastfeeding women living with HIV, regardless of their CD4 cell count.

It is anticipated that the implementation of all the 2016 recommendations at the national and international levels will have important implications for programme priority-setting, funding, and service delivery. The 2016 guidelines also underscore the need for differentiated approaches to care for people who are stable on ART, such as reducing the frequency of clinic visits and community ART distribution. Such efficiencies are essential if countries with a high burden of HIV infection are to manage their growing numbers of people receiving ART and reduce the burden on people receiving treatment and health facilities.[110]

The WHO expects countries to further accelerate efforts to meet the ambitious Fast-Track Target for 2020, including achieving major reductions in the number of people dying from HIV-linked causes and the 90–90–90 treatment target: ensuring that 90% of PLWH know their HIV status; 90% of PLWH who know their HIV status are accessing treatment; and that 90% of PLWH who are receiving treatment have a suppressed viral load.

Regrettably, most lower income countries (LICs) have been negligent in the provision of research and healthcare services for PLWH.[111] The neglect is influenced and marked by wars, denialism, economic implications and, at times, sheer ignorance.[112] Endless waiting times for interventions, a dearth of new doctors, unhygienic circumstances, corruption, and a host of other problems plague most of these countries' health systems.[113] In contradistinction, problems such as these are virtually absent in the higher income (HICs) and middle income countries (MICs). This is because there are different incentives and influential factors in the LICs and HICs.[114] Low-income countries generally find ARVs to be unaffordable.[115] Despite the lack of

---

110 World Health Organisation, 'Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach 2nd ed' (World Health Organisation 2016) http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1 accessed 15 September 2021.

111 The vast majority of people living with HIV are in low- and middle-income countries. https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics accessed 01 September 2018.

112 Peter Poit, Sarah Russell and Heidi Larson, 'Good Politics, Bad Politics: The Experience of AIDS' (2007) 97(11) American Public Health Association 1934–1936.

113 http://www.dailymaverick.co.za accessed 21 September 2018.

114 http://www.dailymaverick.co.za accessed 21 September 2018.

115 Steven Forsyth, 'The affordability of antiretroviral therapy in developing countries: what policymakers need to know' (Policy unit of AIDSCAP/Family Health International)

funding for the drugs and medicines, the drug safety and efficacy are issues of particular concern, as HIV drugs are not tested on the PLWH in LICs generally.[116] Groups of persons recommended by the WHO for prioritised treatment include:

- sero-positive mothers who have participated in the prevention of parent-to-child transmission (PPTCT) programme;
- sero-positive children younger than 15 years of age; and
- people with AIDS who seek treatment in government hospitals[117]

2.5 Clinical pharmacology relating to HIV and the development of the ARVs

A major consideration of drug utility in human health preservation is premised on a global health care intervention. In the case of HIV, medicines prescribed for the treatment of HIV,[118] such as ARVs, should be examined regarding their use, application, and side-effects.[119] As this chapter examines selected clinical aspects relating to the medical treatment regime for HIV, it is necessary to briefly discuss the origin of the science linked to the development of drugs. Drugs are chemical or non-chemical substances that offer therapeutic options towards the attainment of health. With proper administration, drugs can offer the freedom from life-changing errors and devastating events to medical patients (patients who solely depend on medical treatment).[120]

Pharmacology is the scientific study of drugs and their utility in a human body in relation to health care to promote remission or recovery.[121] It has also been described as an experimental science that stands out as the cornerstone of the drug discovery.[122] The treatment of disease may entail a wide variety of modalities, aimed at removing the causative agent(s), relieving the symptoms, alleviating the suffering and bringing

https://www.equinetafrica.org/sites/default/files/uploads/documents/FORaids.pdf accessed 15 September 2021.

116 Michael Reich and Priya Bery, 'Expanding global access to ARVs: The challenges of prices and patents' (2005) New York Acardemic Press 324-350, 346.

117 World Health Organisation, *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (2 edn WHO Press 2016) 71-150.

118 Currently there are 39 drugs identified for the treatment of HIV. https://www.cdc.gov/mmwr/preview/mmwrhtml/lmrk077.htm accessed 23 July 2018.

119 ARVs are life-sustaining drugs, whose safety and effect depends on a potential inter- and intra-individual genetic variation.

120 Anita Wyne, *et al*, *Pharmacotherapeutics for Nurse Practitioner Prescribers* (2 edn FA Davis Company 2007).7

121 Anita Wyne, *et al*, *Pharmacotherapeutics for Nurse Practitioner Prescribers* (2 edn FA Davis Company 2007).7

122 Anita Wyne, *et al*, *Pharmacotherapeutics for Nurse Practitioner Prescribers* (2 edn FA Davis Company 2007).

about a satisfactory outcome.[123] Most of the afore-mentioned interventions depend on drug use, drug combinations and/ or other therapeutic effects.

With the outbreak of HIV, researchers expedited interim interventions by introducing ARVs medicines, which include AZT, intended to slow down damage to the immune systems of infected persons.[124] AZT, also referred to as Zidovudine, was the first drug introduced to treat HIV infection.[125] Scientists funded by National Institute of Health (NIH) and the National Cancer Institute (NCI) initially developed AZT in 1964 as a potential cancer therapy.[126] The drug, AZT has proved ineffective against cancer and was subsequently shelved, but in the 1980s, was included in a NCI screening programme to identify potential drugs to treat HIV/AIDS. In laboratory tests, it was shown that AZT suppressed HIV replication without damaging normal cells. In February 1985, the National Cancer Institute, under the direction of Dr Samuel Broder, tested AZT and found that it was a potent inhibitor of HIV. The first drug approval for treating AIDS happened in March 1987.[127] The British pharmaceutical company, Burroughs Wellcome, funded a clinical trial to evaluate the drug in persons presenting with advanced AIDS.[128]

Subsequently, a second drug called Deoxycytidine, also a cancer drug, was approved for the treatment of cancer in AIDS, followed by the approval of Stavudine. These drugs remain the cornerstone in the treatment of HIV. The AZT became associated with decreased deaths and opportunistic infections, albeit with serious adverse effects.[129]

The AIDS Clinical Trials Group (ACTG), established in 1987, started work to impact on the well-being and health of persons infected with HIV-1, with the objective of PMTCT of HIV. The PMTCT project was geared towards saving the unborn child from an HIV infected mother. The purpose of the ACTG group of researchers was to broaden the scope of the AIDS research effort of the National Institute of Allergy and

---

123 Gustav Schellack, Pharmacology in Clinical Practice - Application Made Easy for Nurses and Allied Health Professionals (2 edn Juta Books 2010) 3.

124 http://www.aidsmap.com/resources/treatmentsdirectory/drugs/Zidovudine-AZT-iRetroviri/page/1730919/ accessed 22 October 2018.

125 The NIAID-supported National Cooperative Drug Discovery Group Program for the Treatment of AIDS (NCDDG-AIDS) and have provided a framework for scientists from academia, industry, and government to collaborate on research related to identify and develop of new drugs.

126 The drug AZT or Retrovir as referred to by Dr. Jerome Horowitz, was originally developed in 1964 as a possible treatment for cancer. https://aidsinfo.nih.gov/news/274/approval-of-azt accessed 22 October 2018.

127 https://aidsinfo.nih.gov/news/274/approval-of-azt accessed 22 October 2018.

128 https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development accessed 22 October 2018.

129 http://www.virusmyth.com/aids/hiv/abazt2.htm accessed 22 October 2018.

Infectious Diseases (NIAID). [130] The ACTG's clinical trial established a lower therapeutic dosage of AZT, helping to reduce some of the drug's serious side-effects. The pivotal ACTG 019 trial investigated whether it was beneficial to put people living with HIV on AZT before they progressed to AIDS.[131] The ACTG 019 clinical trial showed that AZT effectively delayed the onset of AIDS in asymptomatic people with HIV, marking the first demonstration of HIV infection treatment. However, in their review paper, "Mitochondrial toxicity of antiviral drugs" published in *Nature Medicine* in 1995, Lewis and Dalakis note that "in some cases, reversal of symptoms corresponds to cessation of therapy; in others toxicity persists".[132] Another adverse drug reaction associated with AZT that was the reported case of a 24-year-old woman who presented with a history of progressive leg weakness and difficulty in walking.[133]

After a protracted debate on the efficacy and safety of ARVs and denialism regarding the treatment of HIV in some countries, it became apparent that the efforts that followed the 1994 revealed that the administration of Zidovudine during pregnancy could reduce the rate of vertical PMTCT through AZT treatment by two thirds.[134] Currently, there are over 39 other ARVs (single and combination drugs) available in six categories.[135] These categories are:

- NRTIs (nucleoside reverse transcriptase inhibitors);
- NNRTIs (non-nucleoside reverse transcriptase inhibitors);
- Protease inhibitors;
- The new fusion inhibitors;
- Entry inhibitors-CCR5 co-receptor antagonists; and
- HIV integrase strand transfer inhibitors,[136] which belongs to a class of drugs known as nucleoside reverse transcriptase inhibitors referred to above, or NRTIs.

---

130 The ACTG establishes and supports the largest Network of expert clinical and translational investigators and therapeutic clinical trials units in the world, including sites in resource-limited countries.

131 National Institutes of Allergy and Infectious Diseases, 'Antiretroviral Drug Discovery and Development' (NIH 2018). https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development accessed 07 December 2022.

132 Anthony Brink, 'Debating AZT and Heavenly Remedies' (Mitochondrial toxicity of antiviral drugs in Nature Medicine 1995) https://www.virusmyth.com/aids/hiv/abazt2.htm accessed 22 October 2018.

133 JS Le Quintrec and JL Le Quintrec 'Drug-induced myopathies' (1991) 5 Baillière's Clinical Rheumatology 21-38.

134 National Department of Health (2017) http://www.health.gov.za/ accessed 22 October 2018.

135 List of ARV drugs in South Africa. https://safacts.co.za/list-of-arv-drugs-in-south-africa-2/ accessed 19 October 2022.

136 The 2018 list supplied by WHO includes the following drugs: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r= atazanavir/ritonavir; BID = twice daily; CD4 = CD4 T lymphocyte; DRV = darunavir; DRV/c =

The NRTIs were the first drug types available for treating HIV. They are effective, powerful, and important medications for treating HIV when combined with other drugs.[137]

As health research advances, so does the study of drug reactions with the assistance of biochemistry and medicinal chemistry. It is common knowledge that contemporary drugs include chemical and/ or non-chemical substances used to cure, stabilise, prevent, diagnose and treat patients in a health care situation. Common examples of non-chemical drugs entail herbs such as Moringa and Marijuana. Opinions about marijuana in the medical community continue to evolve as empirical evidence demonstrates both its clinical benefits and the potential for harm.[138]

Pharmaceutical products aimed at improving health and quality of life for people living with HIV (PLWH) are manufactured on a scale unrivalled by any other medical interventions.[139] Although different pharmaceutical companies manufacture ARVs, each country has its own approval body or authority, such as the Food and Drug Administration (FDA) that approves the use of ARVs in the United States of America. In South Africa, the South African Health Products Regulatory Authority (SAHPRA) grants approvals for the manufacturing of the HIV drugs.[140]

Therefore, pharmaceutical companies in South Africa and the United States need to align their HIV treatment research with the requirements of FDA and SAHPRA respectively. For this reason, drug manufacturing and improvement has become an ongoing concern that necessitates regular research accompanied by approvals from the relevant stakeholders. Pharmaceutical research requires huge budgets and is governed by laws and policies which are a demonstration of a relevant ethical and legal framework.[141] In addition to having an acceptable safety profile, an investigational drug needs to display beneficial therapeutic effects for it to receive marketing approval,

---

darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumara.

137 https://www.hiv.va.gov/patient/treat/nrtis.asp accessed 22 October 2018.

138 The legal status of Marijuana is ever evolving, as is the clinical understanding of the drug's role in the treatment for HIV.

139 Rick Turner J, *New Drug Development: An Introduction to Clinical Trials* (2 edn Springer Verlag New York 2010).

140 SAHPRA came into existence in 2018. This means that South Africa's old regulatory authority, the Medicines Control Council (MCC), no longer exists.

141 Jaiprakash Bhuma and Kuldip Singh Sangwan 'Lean manufacturing: literature review and research issues' (2014) 34 International Journal of Operations & Production Management 876-940.

that is, it needs to have a favourable benefit–risk profile[142] geared towards personalised medicine in the treatment of HIV.

It is noteworthy that those who receive the antiretroviral therapy (ART) respond and conform to the treatment in varying ways. Worth of note further is the fact that there are identifiable consequences regarding ARVs that can both be beneficial and/ or detrimental to recipients of the treatment for HIV. However, it is recognised that synergistic responses to the drugs are based on individualistic genetic and genomic variants.[143]

2.6 The role of epidemiology in the treatment of HIV and AIDS

Epidemiology is the study of the frequency of, and reasons for disease occurrence in different groups. Furthermore, epidemiological information assists with the development of plans and strategies to prevent illness and serves as a guide to the management of patients in whom disease has already developed.[144]

The 1962 Thalidomide disaster illustrates the impact of serious adverse events following a specific drug. The Thalidomide drug was promoted and administered as a sedative and anti-emetic medicine in pregnant women. However, the medicine presented side-effects leading to severe birth defects in unborn children.[145] The Thalidomide tragedy is regarded as the bedrock for the international acknowledgement of ADRs. International and national regulatory frameworks for the manufacture, distribution and administration of medicines need to ensure standards of safety, efficacy and quality. Both the Medicines and Related Substances Control Act,[146] and the National Adverse Drug Event Monitoring Centre (NADEMC), enable the monitoring of ADRs through a unit of SAHPRA, which is on par with similar mechanisms in other international jurisdictions.[147] The above institutions are mostly concerned with the

---

142 JR Turner, *New drug development: An Introduction to Clinical Trials* (2 edn New York: Springer 2019) 165-193.

143 Mary Fowler, Susan Fiscus, and Judith Curriere, 'Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention' (2016) 375(18) New England Journal of Medicine 1726-1737.

144 Columbia Mailman School of Public Health, 'What is epidemiology?' (Public Health, 21 October 2020). https://www.publichealth.columbia.edu/public-health-now/news/what-epidemiology accessed 17 September 2021.

145 José Augusto Leandro, 'Risk-free rest and sleep: Jornal do Médico (Portugal) and the thalidomide disaster, 1960-1962' (2020) 27(1) Scientific Electronic Library Online https://doi.org/10.1590/S0104-59702020000100002 accessed 14 October 2021.

146 Medicines and Related Substances Control Act 101 of 1965.

147 Hasumati Rahalkar, Hacer Coskun Cetintas and Sam Salek , 'Quality, Non-clinical and Clinical Considerations for Biosimilar Monoclonal Antibody Development: EU, WHO, USA, Canada, and BRICS-TM Regulatory Guidelines' (Pharmacol 28 September 2018) https://doi.org/10.3389/fphar.2018.01079 accessed 14 October 2021.

post-ADRs strategies of pharmacovigilance, whereas PGx proposes a pre-ADRs strategy.[148]

Pharmacovigilance is the process of "looking back" after the manufacturing and administration of medicine to assess drug safety and efficacy.[149] Following pharmacovigilance requirements, drug manufacturers are required to attach a comprehensive leaflet wherein side-effects and other relevant information is supplied.[150]

Regarding the treatment of HIV, the efficacy challenge of antiretroviral therapy originates from the emergence of resistant HIV-1 mutants with reduced susceptibility to antiretroviral drugs.[151] During the course of early HIV infection, patients may present with bacterial pneumonias, which generally respond readily to antibiotics. However, treatment could be frustrated by emerging opportunistic infections; for example:

- patients with HIV infection appear to be particularly prone to infections with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenza;*
- later, and with the onset of immune suppression, patients may develop opportunistic pulmonary infections, the most important of which is Pulmonary Tuberculosis; and
- as cell-mediated immunity deteriorates, patients may develop life-threatening opportunistic infections, such as Pneumocystis Pneumonia (PCP) and severe fungal and viral pneumonias.

Moreover, pharmacotherapy (medical treatment by means of medicine) of patients infected with HIV is uniquely difficult because a great number of co-morbidities increase polypharmacy (the concurrent use of multiple medications by a patient) and the risk for drug-to-drug interactions. Some drug combinations are contraindicated – which means patients should not ingest them together, since they may cause problems such as serious side-effects, or interactions which could render one or both drugs ineffective or toxic. [152] Drug-metabolising enzymes and drug transporters regulate drug

148 L Härmark and AC van Grootheest, 'Pharmacovigilance: methods, recent developments and future perspectives' (2008) 64(1) Eur J Clin Pharmacol 743–752.

149 S Rodríguez, *et al,* 'Pharmacovigilance of Biopharmaceuticals in Rheumatic Diseases, Adverse Events, Evolution, and Perspective: An Overview' (2020) 8(9) Biomedicines 303.

150 Lawrence Gould, 'Practical pharmacovigilance analysis strategies' (01 November 2002) https://doi.org/10.1002/pds.771 accessed 04 October 2021.

151 The ability of HIV to mutate and reproduce itself in the presence of antiretroviral drugs is called HIV drug resistance (HIVDR). https://www.who.int/hiv/topics/drugresistance/en/ accessed 19 October 2018.

152 http://www.aidsmap.com/Drug-interactions/page/2841941 accessed 22 October 2018.

access to the systemic circulation, target cells, and sanctuary sites.[153] These factors, which determine drug exposure, along with the emergence of mutations conferring resistance to HIV medications, could explain variability in efficacy and adverse drug reactions associated with antiretroviral drugs.[154] Furthermore, side-effects from antiretroviral drugs may include:[155]

- hypersensitivity or allergic reactions, with symptoms such as fever, nausea, and vomiting; and
- bleeding, bone loss, heart disease, high blood sugar and diabetes, lactic acidosis (high lactic acid levels in the blood), kidney, liver, or pancreas damage.

Unexpected serious adverse reactions (SUSARs) are also common among ARVs.[156] Hence, continued insight into serious adverse events (SAEs) is critical in order to provide adequate information on the safety and efficacy of ARVs.[157]

As explained in more detail below, although the biomedical model has initially been considered as the appropriate model for the development of ARVs,[158] international pharmaceutical companies embarking on the manufacturing of ARVs slowly began to realise that there should be closer attention on the importance of PGx in the development of ARVs.[159]

2.7 Efficacy and safety of antiretroviral treatment

As alluded above, treatment ramifications have arisen regarding ARVs, including ADRs, which may be ascribed to the manufacturing and administering of the drugs without proper consideration of human enzyme responses to the drugs.[160] The approval of drugs used as medicine for HIV, similar to other drugs requiring approval before their release into the market, has to follow prescribed regulatory pathways, including clinical trials and other relevant research processes. Clinical trials are

---

153 Daniel Jonker, *et al*, 'Towards a Mechanism-Based Analysis of Pharmacodynamic Drug–Drug Interactions in Vivo' (2005) 106 Pharmacology & Therapeutics1-18.

154 Veronique Michaud, *et al*, 'The Dual Role of Pharmacogenetics in HIV Treatment: Mutations and Polymorphisms Regulating Antiretroviral Drug Resistance and Disposition' (2012) 64(3) Pharmacological Reviews 803-833.

155 Jayne Leonard, 'How does antiretroviral therapy work?' (Medical News Today 29 November 2020) https://www.medicalnewstoday.com/articles/324013 accessed 17 September 2021.

156 E Pietraszkiewicz ,*et al*, 'The Suspected Unexpected and Serious Adverse events of Antiretroviral Drugs used as HIV Prophylaxis in HIV Uninfected Persons' (2014) 17(3) Journal of the International AIDS Society 19733.

157 https://www.healthline.com/health/hiv-aids/antiretroviral-drugs-side-effects-adherence accessed 09 July 2018.

158 https://aidsinfo.nih.gov/news/274/approval-of-azt accessed 22 October 2018.

159 S Rodríguez-Nóvoa, *et al*, 'Overview of the Pharmacogenetics of HIV therapy' (2006) 6 Pharmacogenomics Journal 234–245.

160 Daniel Jonker, *et al,* 'Towards a Mechanism-Based Analysis of Pharmacodynamic Drug–Drug Interactions in Vivo' (2005) 106 Pharmacology & Therapeutics1-18.

research studies performed in people and are aimed at evaluating a medical, surgical, or behavioural intervention.[161] They are the primary way that researchers find out if a new treatment, like a new drug or diet or medical device (for example, a pacemaker) is safe and effective in people. Often a clinical trial is used to learn if a new treatment is more effective and/or has less harmful side effects than the standard treatment. The approval pathways of drugs used as medicine for HIV encompass the following:

- Phase I studies targeting drug safety profiles, including the potential safe dose range. It also determines pharmacokinetics[162] and pharmacodynamics,[163] optimal methods of drug administration, as well as possible pharmacovigilance (tracking of Adverse Drug Reactions (ADRs)).[164]
- Phase II tests focusing on determining the therapeutic effectiveness of the compound in subjects, with further attention to safety. The results of Phase II are used to establish the parameters of Phase III, especially the compound's clinically effective dose.[165]
- The intended design of Phase III is to determine and to establish whether the benefits of a treatment with the tested compound is significant enough to outweigh the risks. The tests used in Phase III provide the basis for approval of the drug and this should be extremely thorough and meet rigorous standards of safety, quality, and efficacy.[166] Hence, the manufactured drug is mostly a one-size-fit-all product.[167]
- Phase IV studies taking place after the medicine has received regulatory approval (market authorisation) and are designed to check the drug's performance in real life scenarios and to study the long-term risks and benefits of using the drugs and to discover rare side-effects.[168]

---

161 https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies accessed 19 September 2018.

162 Pharmacokinetic interactions, strongly influence the magnitude of drug responses based on dose- and concentration, that is, how a drug is absorbed, distributed, metabolised and excreted. Daniel Jonker, *et al*, 'Towards a Mechanism-Based Analysis of Pharmacodynamic Drug–Drug Interactions in Vivo' (2005) 106 Pharmacology & Therapeutics 1-18.

163 Pharmacodynamics refers to the study of the effects of drugs on the body, in particular, the duration of its action. It describes drug-receptor interaction. Anita Wyne, *et al*, *Pharmacotherapeutics for Nurse Practitioner Prescribers* (2 edn FA Davis Company 2007) 14.

164 Pharmacovigilance is defined by WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/ accessed 19 September 2018.

165 https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm340007.pdf. accessed 19 September 2018.

166 Gerlie Gieser, 'Clinical Pharmacology 1: Phase 1 Studies and Early Drug Development' (2012) Office of Clinical Pharmacology.

167 Andrew Marshall, 'Getting the Right Drug into the Right Patient' (1997) 15 Nature Biotechnology 1249-1252.

168 Charles Grudzinskas, 'Chapter 33 - Design of Clinical Development Programs' (2007) Principles of Clinical Pharmacology 501-517

Adverse drug reactions could be classified into five types or classes, namely: A to E.[169] The Class A and Class B types seem to be mild and more easily manageable. However, the three classifications of C, D and E are likely to impact on PLWH in that the reactions occur, based on inappropriately long term usage (Class C); or at a critical phase of the disease or pregnancy (Class D), or because treatment is interrupted abruptly or is provided together with other drugs (Class E).[170] The latter ADRs will persist in the treatment of HIV, as most ARVs are compounded using a combination of drugs.[171] However, some authors believe that a combination of drugs in the treatment of HIV may reduce the risk of resistance to the ARVs, although conceding that 'intolerance' and 'idiosyncrasy' as part of the causes of adverse reactions are common with the use of ARVs.[172]

In the context of medicine, idiosyncrasy is a form of adverse drug response, described as an inherited abnormal response to drugs mediated by single genes in the human body.[173] It is for this reason that gene studies are critically important in investigating a possible relationship between biochemical and enzymatic mechanisms. Despite the rigorous processes required for developing new medicines and the focus on safety and efficacy, ARVs and the reported ADRs remain a concern, especially in the South African context. [174] Several factors may predispose individuals to adverse effects of ARV medications, such as:

- concomitant use of medications with overlapping and additive toxicities;
- comorbid conditions that increase the risk of or exacerbate adverse effects (e.g., alcoholism or co-infection with viral Hepatitis 2 may increase the risk of hepatotoxicity);
- drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications;
- genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction; and
- neuropsychiatric toxicity.[175]

---

169 PN Bennett and MJ Brown, *Clinical Pharmacology* (9 edn McGraw-Hill Medical 2003) 139.

170 PN Bennett and MJ Brown, *Clinical Pharmacology* (9 edn McGraw-Hill Medical 2003) 139.

171 PN Bennett and MJ Brown, *Clinical Pharmacology* 139.

172 PN Bennett and MJ Brown, *Clinical Pharmacology* 136. Refer to intolerance as a low threshold to the normal pharmacodynamics and idiosyncrasy is defined as an inherent qualitative abnormal reaction to a drug due to neglect of pharmacogenomics.

173 Daniel Jonker, *et al,* 'Towards a Mechanism-Based Analysis of Pharmacodynamic Drug–Drug Interactions in Vivo' (2005) 106 Pharmacology & Therapeutics1-18.

174 https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/31/adverse-effects-of-antiretroviral-agents accessed 17 October 2017.

175 NIH provides this list of Adverse Effects of Antiretroviral Agents.

Genetic factors may also present as one of the factors that predispose PLWH to adverse reactions.[176] Since the listed factors are made available to South African patients, the question arises as to whether the genetic profiles of patients have been a consideration in the development of the drugs, as well as their administration.[177]

The University of the Witwatersrand's HIV Genotyping laboratory established in 2004, is involved in research that provides clinicians with valuable knowledge on HIV-1 drug resistance. One such project is the SATuRN project, which consists of a network established in South Africa to perform surveillance testing on HIV-1 drug resistance in the public sector.[178]

At the time of writing this thesis (2021-2022), the genetic characteristics that influence the pharmacokinetics and the pharmacodynamics of drugs are still poorly understood in African populations, including South Africa; thereby limiting treatment optimisation.[179] For example, identified gene variants may be useful for screening HIV-infected patients prior to treatment. Furthermore, the study of additional pharmacogenomics parameters, such as clinical response to treatment or the ability to predict treatment failure, need to be carried out.[180]

Human genome sequencing provides a framework for understanding the role of genetic variation on the development and prevalence of disease and human evolution.[181] Although there are several different types of polymorphic markers. A "polymorphic marker" can be described as a variation (which may arise due to mutation or alteration in the genomic loci) that can be observed. A genetic marker may be a short DNA sequence, such as a sequence surrounding a single base-pair change (single nucleotide polymorphism, SNP), or a long one, such as minisatellites.[182] Most

---

176 PE Tarr and A Telenti, 'Toxicogenetics of Antiretroviral Therapy: Genetic Factors that Contribute to Metabolic Complications' (2007) 12(7) Antiviral Therapy 999-1013; See also Sumeshni Birbal, *et al,* 'Adverse drug reactions associated with antiretroviral therapy in South Africa' (2016) 15(3) African Journal of AIDS Research 243-248.

177 U Mehta, *et al*, 'Pharmacovigilance: A public health priority for South Africa' (2017) SAHR 125-133.

178 HIV Genotyping Laboratory (Witwatersrand University) https://www.wits.ac.za/pathology/divisions/molecular-medicine--haematology/research-and-analytical-services/hiv--haematology-molecular-diagnostics-unit/hiv-genotyping/ accessed 17 January 2019.

179 Danai Tavonga Zhou, *et al*, 'Emerging Role of Pharmacogenomics in HIV Research in Africa' (2021)16(5) Future Virology.

180 Zhou, *et al*, 'Emerging Role of Pharmacogenomics in HIV Research in Africa' (2021) 16(5) Future Virology.

181 ES Lander, *et al*, 'Initial sequencing and analysis of the human genome' (2001) Macmillan Publishers Ltd 860-921; Craig Venter, et al, 'The Sequence of the Human Genome' (2001) 219 Science 1304-1351.

182 See https://medicaldictionary.thefreedictionary.com/polymorphic+genetic+marker accessed 17 January 2019.

attention recently has focused on single nucleotide polymorphisms (SNPs)[183] and the potential for using these to determine the individual drug response profile. The role of pharmacogenomics in the treatment of HIV has become critically important, as it is involved with the study of the role of the human genome in drug response, analysing how the genetic makeup of an individual affects his or her response to specific drugs.

The WHO Programme for International Drug Monitoring consists of more than 150 countries that share the vision of safer and more effective use of medicines and work together to monitor and identify the harm caused by medicines, to reduce the risks to patients and to establish worldwide pharmacovigilance standards and systems.[184] In South Africa, the two functions are the responsibility of the South African Health Products Regulatory Authority (SAPHRA), which was established in 2018.

The SAHPRA (previously the Medicines Control Council (MCC), is a statutory body that regulated the performance of clinical trials and registration of medicines and medical devices for use in specific diseases. [185] The legislation that governs this monitoring process is, as stated above, the MRSA.[186] In April 2021, SAHPRA launched its Med Safety App, which is a mobile application (App) that is designed to simplify and promote the reporting of suspected adverse drug reactions (ADRs).[187] It is hoped that the establishment of South African Medical Research Council's Genomics Centre, which oversees the 'latest sequencing technology and cutting-edge facility',[188] may lead the way for the implementation of PGx in South Africa.

2.8 Role and significance of PGx

The application of personalised medicine in the field of HIV treatment is critically dependant on PGx in the production of patient compatible ARVs. Personalised medicine in HIV treatment is diametrically opposed to the conventional notion of mass production (one size fits all)[189] drugs. Doctors conventionally prescribe medicine based

---

183 https://ghr.nlm.nih.gov/primer/genomicresearch/snp accessed 19 October 2018.

184 https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring/ accessed17 September 2021.

185 SAHPRA responsible for ensuring that all clinical trials of both non-registered medicines and new indications of registered medicines comply with the necessary requirements for safety, quality and efficacy. http://www.sanctr.gov.za/YourRights/TheMedicinesControlCouncil/tabid/176/Default.aspx accessed 13 September 2018.

186 Medicines and Related Substances Act 101 of 1965.

187 https://www.sahpra.org.za/press-releases/sahpra-launches-the-med-safety-app-for-self-reporting-of-suspected-adverse-drug-reactions-by-the-public-and-healthcare-professionals/ accessed 19 October 2022.

188 https://www.samrc.ac.za/innovation/genomics-centre accessed 25 August 2022

189 The notion of 'one-size-fits-all drugs' is the direct opposite of "Personalised medicine and is often used interchangeably with, precision medicine, stratified medicine, targeted medicine, and pharmacogenomics." National Academy of Sciences.

not only on the diagnosis, but also considering a patient's age, weight, sex, and liver and kidney function. For a few drugs, researchers have identified gene variants that affect how people respond. In these cases, doctors can select the best medication and dose for each patient.

For this reason, the science of PGx should inform the treatment for PLWH, considering the range of medication that is prescribed as part of HIV treatment. PGx is an inseparable component of pharmacology to which genetic and genomic factors become necessary to determine human responses to drug therapy. Regrettably, the past few decades have witnessed the blockbuster production of ART, which does not make room for the development of personalised medicine.

In the treatment of the individual patient, the vision is to achieve the best possible balance between benefit and harm. Therefore, precision therapy relies upon the identification and characterisation of risk factors as a pre-ART endeavour to lessen ADRs.[190] On a global scale, assisting with the identification and recording of ADRs, is the WHO's global side-effects database, known as Vigibase.[191] As the largest database of its kind in the world, it references more than 30 million reports of suspected adverse effects of medicines since 1968, submitted by member countries of the WHO's International Programme for Drug Monitoring (PIDM).

In order to understand the difference between the standard of care with regard to medical vis-à-vis pharmaceutical care, it is necessary to distinguish between the forms of control for medical practice on the one hand, and pharmaceutical practice on the other hand. The term "pharmaceutical care", which is relevant to PLWH, refers to "responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life", which include to cure disease; eliminate or reduce symptoms; delay or slow down disease progress or to prevent disease or symptoms.[192]

The SAHPRA guidelines define pharmacovigilance as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects

---

https://www.thepharmaletter.com/article/special-report-personalized-medicine accessed 16 October 2021.

190 Sandberg L, *et al,* 'Risk Factor Considerations in Statistical Signal Detection: Using Subgroup Disproportionality to Uncover Risk Groups for Adverse Drug Reactions in VigiBase' (PubMed,) https://doi.org/10.1007/s40264-020-00957-w accessed 05 March 2019.

191 Sandberg, *et al* 'Risk Factor Considerations in Statistical Signal Detection: Using Subgroup Disproportionality to Uncover Risk Groups for Adverse Drug Reactions in VigiBase' (PubMed,) https://doi.org/10.1007/s40264-020-00957-w accessed 05 March 2019.

192 Tietze KJ. Introduction: the practice of clinical pharmacy. In: Tietze KJ (ed). *Clinical skills for pharmacists: A patient-focused approach* (third ed) Missouri: Elsevier Mosby (2012) at 1.

or any other drug-related problem".[193] In relation to HIV treatment, proper pharmacovigilance of ARV usage in PLWH is required. As discussed earlier in this chapter, the ADRs experienced by PLWH are marked by adverse events that are potentially life threatening; the drugs may cause malignancy or result in permanent disability or birth defects especially in neonates; and could cause organ toxicity that could lead to death.[194]

Moreover, in the context of HIV research, questions arising are: what type of research on PGx should be permitted in South Africa; whether regulations for gene profiling of PLWH for purposes of PGx exist, and finally, what role genetics should play in assessing the complexities surrounding the procurement and manufacturing of ARVs in South Africa. The economic dynamics of resources and expertise are serious considerations to be explored regarding the implementation of PGx.

The next section briefly traces the origins of PGx, in order to provide better insight into the evolution of the fusion between the domains of pharmacology and genomics.

2.8.1 A historical overview of PGx

It is interesting to note that already in 510 B.C., Pythagoras recognised the dangers (and adverse reaction) of some individuals to the 'fava bean' whilst working in Croton, Southern Italy. Nowadays, the bean is known for its adverse reaction of haemolytic anaemia in those who are deficient in glucose-6-phosphate dehydrogenase.[195] Pythagoras' findings led to further investigations on how a human body adversely reacts to certain foods or drugs because of their genetic make-up, thus laying a foundation to personalised reactions to drugs.[196]

Gregor Mendel, known as the "Father of Genetics,"[197] showed that the inheritance of certain traits in pea plants follow patterns, which assisted in the study of heredity. Although his theory did not specifically address the human species, his research

---

193 SAHPRA, 'Pharmacovigilance systems' (May 2022). https://www.sahpra.org.za/wp-content/uploads/2022/05/SAHPGL-CEM-PV-02_Pharmacovigilance-Systems_Version-1.0.pdf accessed 28 October 2022.

194 S Zondi and P Naidoo, 'Perceptions, Practices and Barriers to Reporting of Adverse Drug Reactions Among HIV Infected Patients and their Doctors in 3 Public Sector Hospitals of the Ethekwini Metropolitan, Kwa-Zulu Natal: A Cross Sectional and Retrospective Analysis' (2022) 22 BMC Health Services Research 1054.

195 http://www.lateralmag.com/columns/gene-dosage/pythagoras-the-fava-of-pharmacogenomic accessed 10 October 2018.

196 http://www.lateralmag.com/columns/gene-dosage/pythagoras-the-fava-of-pharmacogenomic accessed 22 October 2018.

197 Rama Singh, 'Limits of imagination: the 150th Anniversary of Mendel's Laws, and why Mendel failed to see the importance of his discovery for Darwin's theory of evolution' (2015) 58(09) Genome https://doi.org/10.1139/gen-2015-0107 accessed 14 October 2021.

demonstrated how genetic variations are responsible for the definition of certain traits in living organisms.[198] Mendel's discovery sets the dais for genetic and genomic studies, which is currently pursued across the globe in many research institutions, of which the Human Genome Project may be the best known.[199]

In 1905, William Bateson, Edith Rebecca Saunders, and Reginald Punnett[200] pursued the study of genes by examining flower colour and pollen shape in sweet pea plants. Shortly afterwards in 1911, Alfred Sturtevant undertook a study to map the locations of the fruit fly (*Drosophila melanogaster*) genes.[201] Snyder's original study in 1932 of the 'phenylthiourea non-taster' phenotype,[202] which refers to the inherited trait to taste (or not taste) phenylthiocarbamide (a bitter compound, found to be inherited as an autosomal recessive trait) is often credited as signalling the dawn of modern pharmacogenetics.

The term, "pharmacogenetics" was invented in 1959 by Friedrich Vogel, a German human geneticist who established the highly regarded journal, *Human Genetics*. The recognition of adverse drug reactions led to an increase in human genome studies and the subsequent introduction of human biobanks. For the sake of brevity, an overview of key historical events that marked the development of PGx is depicted in Table 2.1 below: [203]

Table 2.1: Overview of key historical events marking development of PGx

Year	Individual(s)	Landmark
510 BC	Pythagoras	Recognition of the dangers of ingesting fava beans, later characterised to be due to deficiency of G6PD
1866	Mendel	Establishment of the rules of heredity
1906	Garrod	Publication of '*Inborn Errors of Metabolism*'
1932	Snyder	Characterisation of the 'phenylthiourea non-taster' as an autosomal recessive trait
1956	Carson *et al.*	Discovery of glucose-6-phosphate dehydrogenase deficiency

198 http://www.dnaftb.org/1/bio.html accessed 22 October 2018.

199 David Bentley, 'The Human Genome Project—An Overview' (2000) 20(3) Medicinal Research Reviews https://doi.org/10.1002/(SICI)1098-1128(200005)20:3<189::AID-MED2>3.0.CO;2-%23 accessed 14 October 2021.

200 https://archive.org/stream/bookbulletin3740sanf/bookbulletin3740sanf_djvu.txt accessed 22 October 2018.

201 http://www.dnaftb.org/11/bio.html accessed 22 October 2018.

202 LH Snyder, 'Inherited Taste Deficiency' (1931) 74(1910) Science 151–152.

203 Munir Pirmohamed, 'Pharmacogenetics and Pharmacogenomics' (2001) 52(4) British Journal of Clinical Pharmacology 345–347.

Year	Individual(s)	Landmark
510 BC	Pythagoras	Recognition of the dangers of ingesting fava beans, later characterised to be due to deficiency of G6PD
1957	Motulsky	Further refined the concept that inherited defects of metabolism may explain individual differences in drug responses
1957	Kalow & Genest	Characterisation of serum cholinesterase deficiency
1957	Vogel	Coined the term pharmacogenetics
1960	Price Evans	Characterisation of acetylator polymorphism
1962	Kalow	Publication of *Pharmacogenetics – Heredity and the Response to Drugs*
1977/79	Mahgoub *et al.* and Eichelbaum *et al.*	Discovery of the polymorphism in debrisoquine hydroxylase sparteine oxidase
1988	Gonzalez *et al.*	Characterisation of the genetic defect in debrisoquine hydroxylase, later termed *CYP2D6*
1988–2000	Various	Identification of specific polymorphisms in various Phase I and Phase II drug metabolising enzymes
2000	Public-private partnership	Completion of the first draft of the human genome
2000	The International SNP Map Working Group	Completion of map of human genome sequence variation containing 1.42 million SNPs

Of all these landmarks, Mendel's findings undoubtedly paved the way to the study of human genes. As the study of inheritance expanded beyond the seven traits Mendel initially examined, he further focussed on organisms other than pea plants, leading biologists to notice a variety of relationships between alleles[204] that code for the same trait. These allelic interactions were not exclusively recessive or dominant, and they greatly enriched our understanding of how genotype leads to phenotype,[205] thereby confirming the principle of gene inheritance, through either partial, complete co-dominance and over-dominance.

The brief overview above emphasises the need for gene studies and a clear understanding of the individual responses to drugs resulting from a person's genetic profile or makeup before drug development commences. Genotyping and phenotyping

[204] Allele is one of two alternative forms of a gene. https://www.nature.com/scitable/definition/allele-48/ accessed 07 December 2022.

[205] Condition where the heterozygote is better adapted than either homozygote. See - I Miko, 'Genetic dominance: genotype-phenotype relationships' (2008) 1(1) Nature Education 140.

processes[206] are used to determine the genetic profiles of a person or specific group. It was the Human Genome project that catapulted the study of the human genome towards pharmacogenomics.[207] The Human Genome Project was a concerted public effort between the United States National Institutes of Health (NIH) and the Department of Energy, joined by international partners in the quest to sequence all three billion letters, or base pairs, in the human genome, which is the complete set of DNA in the human body. The project started in 1990 and was completed in April 2003.[208] In order to understand the significance of PGx in the context of HIV treatment, the next section will turn to the role of the interaction between pharmaceuticals and genomics and the development of personalised medicine.

2.8.2 Pharmacogenetics and pharmacogenomics in the context of HIV treatment

As stated previously, pharmacogenetics is the science concerned with the study of genes in relation to how a human body reacts to, or metabolises medication.[209] In HIV patients, genetic testing is expanded to the infected gene to determine the patient's response to ART.[210] Genetic biomarkers, called pharmacogenes, have been identified as specific genetic *loci* on chromosomes which are associated with either positive or adverse drug responses.[211]

When the focus is on the involvement of a gene or a group of genes and its/ their attendant multiple reactions to general medicinal treatment, pharmacogenomics become relevant. While *pharmacogenetics* is largely used in relation to genes determining drug metabolism, *pharmacogenomics* is a broader based term that encompasses all genes in the genome that may determine drug response.[212] Pharmacogenomics emphasise the serious health risks that recipients of mass-produced medication (one-size-fits-all) face, in that these medicines may not only fail as a treatment regime, but also introduce grave health risks in addition.

---

206 https://study.com/academy/lesson/genotyping-phenotyping-definitions-processes-uses.html accessed 22 October 2018.

207 NIH.gov report 2018. https://report.nih.gov/ accessed 22 October 2018.

208 Khoi-Sans and Archbishop Desmond Tutu participated from the South Saharan perspective.

209 In 2006 in Rome, a workshop on international perspectives in pharmacogenetics considered the impact of pharmacogenetics on biomedical innovation and health care.

210 YD Mahnke, *et al*, 'Reconstitution of Peripheral T Cells by Tissue-Derived CCR4+ Central Memory Cells Following HIV-1 Antiretroviral Therapy' (2016) 1(2) Pathog Immun 260–290.

211 DP Campion and FJ Dowell, 'Translating Pharmacogenetics and Pharmacogenomics to the Clinic: Progress in Human and Veterinary Medicine' (Front Vet Sci 11 February 2019) https://doi.org/10.3389/fvets.2019.00022 accessed 03 December 2021.

212 M Pirmohamed, 'Pharmacogenetics and pharmacogenomics.' (2001) 52(4) British Journal of Clinical Pharmacology 345-347.

The focus of this chapter on the assessment of HIV response to drugs based on pharmacogenomics, clarifies that genetics and genomic studies are a highly effective tool for purposes of drug manufacturing and shaping the field of medicine through its potential in realising personalised medicine. Therefore, pharmacogenomics offer hope to those suffering from adverse reactions to drugs treatment for HIV and other disorders associated with opportunistic diseases.

2.9 Personalised medicine

Personalised medicine developed parallel to the fields of PGx and was introduced during the first human genome's sequencing.[213] The National Academy of Sciences (NAS) defines personalised medicine in terms of its objectives, which relate to "the use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment".[214] Similarly, the National Human Genome Research Institute posit that a personalised approach to medicine should include an "individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease."[215] The two aforementioned definitions of personalised medicine complement each other and emphasise the importance the use of the pharmacogenomics for the administration of medicine.

Current areas in which personalised approaches are particularly promising include the fields of oncology, cardiovascular diseases, neurodegenerative diseases, psychiatric disorders, diabetes and obesity, arthritis, pain, and Alzheimer's disease. This personalised-based medicine approach has the potential to provide better health outcomes, improved treatments, and a reduction in toxicity due adverse drug responses. However, at the time of writing this thesis, the development of personalised medicine in the treatment of HIV is still nascent.[216]

In order to deliver health improvements in the treatment of HIV, firmer strides in the field of pharmacogenomics targeting HIV are necessary. The science of genomics in the fields of research and new technologies should be accompanied by changes to the organisation, infrastructure and ethico-legal regulatory framework governing genetic and genomics research in South Africa, as discussed elsewhere in this thesis.

---

213 The information gathered in this project has allowed scientists to make great advances in understanding the differences between people that contribute to health and disease. Genomics Education Programmes- 20 January 2017.

214 Policy Issues in the Development of Personalized Medicine in Oncology Workshop Summary (2010).

215 https://www.genome.gov/ accessed 07 December 2022.

216 Jessica Cusato, *et al*, 'Precision medicine for HIV: where are we?' (2018) 19(2) Pharmacogenomics 145-165.

2.10 Relationship between pharmaceutical medicines and genomics

Chapter Three of this thesis encapsulates the manufacturing of ARVs in the pharmaceutical industry, including the enforcement of IPR in ARVs,[217] which have been in a state of constant flux.[218] New drugs are ushered unremittingly into the South African health market.[219] Equally, with large numbers of patients taking ARVs, the manifestation of ADRs is also unrelenting.[220] As was discussed in Chapter Two, antiretroviral treatments are often accompanied by drug reactions which escalate to ADRs based on a variety of factors, such as a person's genetic composition, responds to the drug.[221] The medicines in the treatment of HIV are supposedly "chosen according to evidence of safety, efficacy and public health relevance."[222] The failure of a prescribed HIV drug to achieve the desired effect of treatment, which instead produces an adverse effect resulting in ADRs, attracts medical malpractice. Medical malpractice occurs when a hospital, doctor, or other health care professional, through a negligent act or omission, causes an injury to a patient. The negligence could be the result of errors in diagnosis, treatment, aftercare, or health management, [223] or even medical negligence as potential legal consequences.[224] To this end, advanced bioinformatics in genomics capabilities is creating opportunities for the rapid integration of drug safety and efficacy into the medical practice towards ushering in the concept of personalised medicine.[225]

Unsurprisingly, clinical pharmacology and drug development have essentially been shaped in part by ADRs.[226] Safety and efficacy are critical requirements in drug development and administration, for both the original and generic drugs,[227] thus

---

217 Article 31 of TRIPS.

218 Hanlie Myburgh, *et al,* 'Implementing 'Universal' Access to Antiretroviral Treatment in South Africa: A Scoping Review on Research Priorities' (2021) 36(6) Health Policy and Planning 923–938.

219 Food and Drug Administration (FDA HIV approved drugs) https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines accessed 6 January 2022

220 http://indexmedicus.afro.who.int/iah/fulltext/incidencepdf.pdf accessed 30 October 2019.

221 MJ Alomar, 'Factors Affecting the Development of Adverse Drug Reactions (Review article)' (2014) 22(2) Saudi Pharm J 83–94.

222 Marie-Paule Kieny, WHO Assistant Director-General for Health Systems and Innovation. Her mission is to improve access to medicines for millions of people in LMICs.

223 https://www.abpla.org/what-is-malpractice accessed 16 October 2019.

224 Daniele Bryden, and Ian Storey, 'Duty of Care and Medical Negligence' (2011) 11(4) Continuing Education in Anaesthesia Critical Care & Pain 124-127.

225 MJ Alomar, 'Factors Affecting the Development of Adverse Drug Reactions (Review article)' (2014) 22(2) Saudi Pharm J 83–94.

226 Pharmacology is the science of drugs https://www.merriam-webster.com/dictionary/pharmacology accessed 16 October 2019.

227 B Kiliç, *Boosting Pharmaceutical Innovation in the Post-TRIPS Era, Real-Life Lessons for the Developing World* (Edward Elgar Publishing 2014) 33. Patented according to the draconian TRIPS regime.

necessitating pharmacovigilance (PV).[228] The World Health Organisation (WHO) defines PV as the "science and activities related to detection, understanding, assessment and prevention of negative effects or any other possible drug-induced problem."[229] The convergence of drug development and administration creates a dangerous combination in the absence of PV and PGx.[230] Therefore, based on the discussion above, the argument for the implementation of PGx is latent to the practice of personalised medicine, which evolves as a protective measure against the consequence of ADRs.[231]

The discussion above alludes to the need for a better understanding of the common variations in human genes in the development of medicines. Scientists understand that ADRs manifest in various aetiologies, such as complications on an underlying disease, coincidental accidents, concomitant medication, intercurrent disease and drug associated effects.[232]

In recent times, scientists across the globe have accelerated research focused on understanding the mechanisms by which genetic variants, discovered through genome-wide association studies by means of sequencing studies, and how these influence the treatment and drug risks in HIV and its related diseases.[233] To this end, rapid and broad sharing of large-scale genetic/ genomic data is critical, similar to the open-science, data-sharing model of the WHO.[234] Genetic and genomic data are generated through, *inter alia*, gene sequencing, which not only confirms the incidence of viruses, but can also identify the genetic variants that exist in the individual that could inform the person's possible reactions to medication and treatment.

As a science, pharmacogenomics presents a challenge to South Africa. This is exacerbated by complexities arising from the application of pharmacogenomics into health care delivery, or differently put, the translation of pharmacogenomics research

---

228 Sten Olsson, Shanthi N Pal and Alex Dodoo, 'Pharmacovigilance in resource-limited countries' (2015) 8(4) Expert Review of Clinical Pharmacology 449-460.

229 Sten Olsson, Shanthi N Pal and Alex Dodoo, 'Pharmacovigilance in resource-limited countries' (2015) 8(4) Expert Review of Clinical Pharmacology 449-460.

230 G Schellack, *Pharmacology in Clinical Practice - Application Made Easy for Nurses and Allied Health Professionals* (2 edn Juta 2010) 12. PGx is based on the premise that no one drug is guaranteed to work the same for every patient.

231 A Aceti, *et at,* 'Pharmacogenetics as a Tool to Tailor Antiretroviral Therapy: A Review' (2015) 4(3) World Journa of Virology 198-208.

232 https://www.ncbi.nlm.nih.gov/books/NBK19932 accessed 22 October 2018.

233 https://www.ncbi.nlm.nih.gov/pubmed/20235850 accessed 22 October 2018.

234 These principles for data-sharing were developed through an international multisectoral consultation held in Geneva in September 2015. The increased provision of surveillance and research data means that central data repositories, inclusive of data curation services, are needed to provide the infrastructure for data sharing. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4794314/ accessed 07 December 2022.

into clinical practice. Ideally, the South African ethico-legal framework should combine aspects of research and clinical practice to create an environment conducive to genomic medicine. In addition, as will be shown, there are some inconsistencies created by the *laissez-faire* approach of the past and current South African government regarding the adverse drug effects of HIV treatment. Such effects could be more purposefully addressed by vigorous pharmacogenomics efforts. These efforts should also be strengthened by a more rigorous and robust ethico-legal framework that will not stifle pharmacogenomics research but be flexible enough to address the unique ethical and legal challenges that may arise.

2.11 Monitoring of adverse drug reactions and clinical trials

South African law, notably Section 14 of the Medicines and Related Substances Act (MRSA), enjoins every medicine to be registered before it may be sold and/ or marketed. Therefore, a medicine registration application should be submitted to SAHPRA for evaluation and approval.[235] When reviewing a marketing application, SAHPRA also considers evidence of efficacy and assessments of safety to facilitate their estimation of an investigational drug's benefit–risk profile. Safety data from clinical trials are also of interest to prescribing physicians. When a clinician prescribes a new treatment to a patient for the first time, both the clinician and the patient are interested in questions such as the following: [236]

- How likely is the patient to experience an adverse drug reaction? (The term adverse drug reaction is employed in a post-marketing setting, rather than the term adverse event (AE) that is used in preapproval clinical trials).
- Are the typical adverse drug reactions temporary or permanent in nature?
- How likely is the patient to suffer an adverse drug reaction that is extremely serious or even life-threatening?
- How might the risk of an adverse drug reaction vary with different doses of the drug?
- How might the risk of an adverse drug reaction change with increasing length of treatment?
- Are there any specific clinical parameters that should be monitored more closely than usual in patients receiving this drug?

---

235 https://www.sahpra.org.za/wp-content/uploads/2020/01/2.01_General-information_-Jul19_v10.pdf accessed 20 September 2021.

236 Rick Turner, *New Drug Development: An Introduction to Clinical Trials* (2 edn Springer Verlag New York 2010) 155.

Clinical registries could be influential in the future monitoring of drug safety and efficacy. In November 2005, the Department of Health issued a statement requiring all new clinical trials to be conducted in the country ought to be registered in the South African National Clinical Trials Register (SANCTR). Registration on SANCTR requires that a trial should be approved by a Research Ethics Committee and adhere to the requirements of the National Regulatory Authorities. Additionally, registries in general are recognised as an important mechanism in quality assurance in terms of identifying and detecting high quality and poor performance in patient management involving the delivery of drugs. Registries can also benchmark national standards, monitor trends in patient characteristics, procedural and drug details and most importantly monitor clinical outcomes through pharmacovigilance programmes.

The key characteristics that enable registries to fulfil these roles include, for example, the collection of a well-defined data set; a standardised process for data collection close to the time of the commencement of treatment; information on patient characteristics, risk factors, procedural or drug details and an agreed set of clinical outcomes (or performance indicators), among others.

Those responsible for the regulation of medicines have specific responsibilities regarding the conduct of clinical trials, as well as ensuring that the rights and health of patients and communities are protected. The approval of clinical trials not only require an evaluation of safety and efficacy of new products under investigation, but adherence to general standards of care and safety of the trial participants is of paramount importance, especially the role of clinical research ethics committees or research ethics committees. The ARVs whose safety-efficacy profiles are often questionable, generally require very careful surveillance when first introduced on a large scale into communities.[237]

2.12 Application of pharmacogenetics and pharmacogenomics in the development of medicines

Additional to the huge benefit of pharmacogenetics in preventing ADRs, pharmacogenetic principles may also be used for inclusion or exclusion criteria when trial participants are enrolled, but only when the metabolic pathway of the drug is known.[238] In the case of exploratory studies, where little is known regarding the manner

---

237 RM Kumar, *et al*, 'Pharmacovigilance and its Importance in Drug Regulation: An Overview' (2011) 3(2) Der Pharmacia Lettre 165-179.
Overview' (2011) 3(2) Der Pharmacia Lettre 165-179.

238 A Surendiran, SC Pradhan and C Adithan, 'Role of Pharmacogenomics in Drug Discovery and Development' (2008) 40(4) Indian Journal Pharmacology 137-43.

in which the drug is metabolised, pharmacogenetic principles cannot be applied for selection of subjects in the early phases of studies.[239] The following table provides an overview of the different applications of pharmacogenomics in the development of medicines.

Table 2.2: Overview of different pharmacogenomics applications in medicine development

Stage	Application of pharmacogenetics/ pharmacogenomics
Drug target Identification	Identification and characterisation of the gene coding for the drug target and to assess the variability
Phase I clinical trial	Patient selection – Inclusion/Exclusion criteria and dose range selection
Phase II clinical trial	Dose modification
Phase III clinical trial	Interpretation of trial results based on pharmacogenetic test results
Phase IV clinical trial	Analysis of reported adverse events with pharmacogenetic tests
Regulatory issues	Requirements for submission of pharmacogenetic data during development and registration of drug

Table 2.2 above illustrates the role of pharmacogenetics and pharmacogenomics in each stage of a clinical trial. Invariably, the table is also an illustration of the application of pharmacogenetic/ pharmacogenomic methods in various stages of drug development:[240]

2.13 Conclusion

The first part of this chapter has focused on the manifestation and treatment of HIV in South Africa. The escalation of South Africa's ART programme has resulted in the country's ART programme constituting the biggest in the world with over 4.4 million people on ARTs. South Africa has also opted for a Rapid HIV Testing strategy, which combines HIV Counselling with Testing (HCT). Rapid tests were thus developed to increase the uptake of HIV testing in both clinical and non-clinical settings by providing same-day HIV results performed by non-laboratory staff with an average of 10 minutes. Thus, rapid tests facilitate early HIV diagnosis with subsequent linkages to care and treatment for HIV infected persons.[241] The testing strategy facilitates early detection of the virus and has also made the delivery of HIV services in South Africa much easier and faster, contributing towards better success in achieving national targets.[242]

239 A Surendiran, SC Pradhan and C Adithan, 'Role of Pharmacogenomics in Drug Discovery and Development' (2008) 40(4) Indian Journal Pharmacology 137-43.

240 A Surendiran, SC Pradhan and C Adithan, (2008) 40(4) Indian Journal Pharmacology 137-43.

241 Aziza Mwisongo, *el al* 'The Quality of Rapid HIV testing in South Africa: An Assessment of Testers' Compliance' (2016) 16(3) African Health Science 646–654.

242 National Department of Health SA, 'HIV and AIDS and STI National Strategic Plan for South Africa 2007–2011' Department of Health (Pretoria, 2007).

However, despite some successes, the main concern that remains relates to achieving the targets for outlying areas; for example, the rural areas.

The study's findings aver that certain demographics have a negative impact based on the following facts: "Of the 4,810 women who had a rapid HIV test, only 166 (3.4%) requested to receive their results on the same day as testing, the remainder opted to return for results at a later appointment. Women with secondary school education were less likely to agree to testing than those with no education".[243]

The emergence of ADRs and SUSARs associated with ARVs, discussed in this chapter, presents a strong argument for an alternative strategy in the development of ARVs that follows a more individually tailored and calibrated response with the assistance of PGx. Personalised medicines are gaining momentum globally[244] as part of a translational research agenda that will enable the development of effective medicines.[245] At present, however, the South African government still does not have effective legal and economic strategies in place to drive the application of pharmacogenomics.[246]

The second part of this chapter has focused on the role and significance of personalised medicine and emphasised that PLWH may have different versions of the same genes, which are an indication of slightly different DNA sequences. The variations in genes for these proteins are the specific focus of pharmacogenomics, because genes may be regarded as "instructions, written in DNA, for building protein molecules",[247] and because proteins affect how medicines work. For example, some proteins include liver enzymes that may chemically change some medicines. Some chemical changes could make the drugs more - or even less active in the body, or more worrying, lead to adverse drug reactions or death.

---

243 Ntombizodumo Mkwanazi, *et al* 'Rapid Testing May not Improve Uptake of HIV Testing and Same Day Results in a Rural South African Community: a cohort study of 12,000 women' (2008) 3(10) PLoS One.

244 Michelle Klein, Masud Parves and Jae-Gook Shin, 'Clinical Implementation of Pharmacogenomics for Personalised Precision Medicine: Barriers and Solutions' (2017) 106 Journal of Pharmaceutical Science 2368-2379.

245 T Kredo, *et al,* 'National Stakeholders' Perceptions of the Processes that Inform the Development of National Clinical Practice Guidelines for Primary Healthcare in South Africa' (2018) 16(1) Health Research Policy and Systems.

246 C Dandara, *et al,* 'African Pharmacogenomics Consortium: Consolidating Pharmacogenomics knowledge, Capacity Development and Translation in Africa' (2019) 2(19) [version 1; peer review: 2 approved]. Open Research Africa.

247 NIH. Pharmacogenomics. https://www.nigms.nih.gov/education/fact-sheets/Pages/pharmacogenomics.aspx (accessed 16 November 2022).

An analysis of the role and significance of PGx in this chapter demonstrates its benefits in the context of clinical trials, specifically regarding issues of safety and efficacy, whose predictability before the advent of pharmacogenetic tools, were very low.[248] The application of pharmacogenomics principles may also assist with the selection of clinical trial participants, specifically with regard to relevant inclusion or exclusion criteria, among others, as was discussed.

There is no doubt that the gradual inclusion of pharmacogenomic studies in drug discovery and development will cause substantial reduction in the expenses involved in the development of medicines, to ensure a safe clinical trial and reduce failures. At the time of writing this thesis, the routine application of PGx in the development of safer and more effective ARVs is still in the future, as its application initially will be associated with high costs, which may not be viable for most LMICs. However, the consideration of cost should not prevent the South African government at this point in time from exploring the benefits of PGx, which, as time will show, will become a standard procedure in the development of ARVs.

The next chapter explores the affordability of, and access of PLWH to ARVs, including the impact of the protection of intellectual property rights in the form of patents in the context of the manufacturing of ARVs.

248 A Surendiran, SC Pradhan, and C Adithan, 'Role of Pharmacogenomics in Drug Discovery and Development' (2008) 40(4) Indian Journal of Pharmacology 137-143.

Chapter 3

Affordability and availability of antiretrovirals in the context of the right of access to health care services

> "It is not from the benevolence of the butcher, the brewer, or the baker that we expect our dinner, but from their regard to their own interest". (Smith A. An Inquiry into the Nature and Causes of the Wealth of Nations (1776))

3.1 Introduction

The above adage aptly captures the tension between the interests of the patent-holder and others that the patent model serves. It is common cause that a gap exists between intellectual property rights (IPR) (which maximises research and development conducted to produce health related treatment on the one hand), and the welfare values of health care through access to pharmaceuticals and the right to access health care services, on the other. Against the broad background of determining the common ground between the economics of health care and the human rights rhetoric of access to health care services, this chapter examines the factors that influence the accessibility, affordability, and availability of ARVs in view of the constitutionally entrenched right of access to health care services in South Africa.

The previous chapter provided an overview of the clinical manifestation of HIV[249] against the background of the development of ARVs in the context of the right to health generally, and more specifically, the right of access to health care services. One of the major global developments in relation to human rights discourses is the recognition that the right to access health care is a fundamental human right,[250] particularly championed by the United Nations (UN). To its credit, addressing and managing HIV has been one of the pharmaceutical industry's more distinguished achievements, despite the turbulence and antagonism that marked the early days of AIDS-related research and development and the industry's relationships with governments, patients and activists.[251]

In Section 1 of the National Health Act, there is an acknowledgement of the right to access health care services; which is also emphasised in Section 27 of the Constitution.[252] Section 27(3) also provides that no one may be refused emergency

---

249 Classified as a virus that attacks the T-Cells in a body. Definition is based on "The History of AIDS". http://www.avert.org accessed 26 February 2019.

250 See, Art 55 of the UN Charter and Art 25(1) of the Universal Declaration of Human Right. The WHO Constitution (1946) envisages "…the highest attainable standard of health as a fundamental right of every human being".

251 https://pharmaphorum.com/sales-marketing/are-dual-arvs-the-new-frontier-in-a-maturin accessed 18 October 2018.

252 Constitution of the Republic of South Africa, 1996.

medical treatment, which arguably would include access to life-saving and chronic health care services in the form of ARVs.[253]

Internationally, AIDS and its related complications reached an all-time high in 1995.[254] The 1990s and early 2000s were marked by efforts of Western pharmaceutical companies and some governments to aggressively limit access to low-cost ARVs for countries on the African continent and the Global South, as presented and discussed in more detail in the current chapter.[255] In 1996, incipient ARV clinical trials became known, followed by the United States' Food and , Administration's (FDA's) approval of ARVs as standard treatment for HIV.[256] The approval of the drugs was accompanied by the notion of IPR on ARVs and the promulgation and overhauling of international treaties, conventions and national patenting laws and policies. The year 1984 marked the advent of battles on patents concerning the discovery of the disease known as HIV (USA, National Cancer Institute (NCI) and the French Pasteur Institute) as well as on the subsequent drugs designed to delay the disease. [257] The denial of access to the ARVs led to thousands of unnecessary deaths, which prompted an improbable group of people repudiated the patenting of the drugs, as discussed in this chapter.[258]

The LMICs in particular, bore the brunt of the crisis of hemming cost factors for treating PLWH.[259] Sub-Saharan African countries belong to the category of LMICs and carry a high burden of HIV, with the transmission of the virus often concentrated amongst key populations, namely: young women, people who inject drugs (PWID), men who have sex with men (MSM), sex workers (SW), transgender (TG) people; as well as prisoners and migrants.[260] Although the transmission of HIV in these groups relate to a range of

---

253 Section 1 of the National Health Act 61 of 2003.

254 AIDS-related deaths occur because of any of more than 20 opportunistic infections or HIV-related cancers. https://www.who.int/features/qa/71/en accessed 18 May 2019.

255 Dylan Mohan Gray, 'Fire in the Blood' (YouTube March 2017) http://www.youtube.com accessed 19 May 2019.

256 In 1996 the FDA approved the first non-nucleoside reverse transcriptase inhibitor (nevirapine), as well as a new viral load test that can measure the level of HIV in a patient's blood. A combination therapy was then made available to HIV/AIDS patients for the first time in the USA, leading to a dramatic decline in AIDS-related deaths.

257 See W William, II Fisher and CP Rigamonti, 'The South Africa AIDS Controversy A case Study in Patent Law and Policy' (Harvard Law School 10 February 2005) https://cyber.harvard.edu/people/tfisher/South%20Africa.pdf accessed 07 December 2022.

258 Hannah Keppler, 'The Untold AIDS Story: How Access to Antiretroviral Drugs was Obstructed in Africa' (The EJBM Blog 01 October 2013) https://theejbm.wordpress.com/2013/10/01/the-untold-aids-story-how-access-to-antiretroviral-drugs-was-obstructed-in-africa/ accessed 05 April 2019.

259 Neil Fantom and Umar Serajuddin, 'The World Bank's Classification of Countries by Income' (World Bank January 2016) http://documents.worldbank.org/curated/en/408581467988942234/pdf/WPS7528.pdf accessed 26 May 2019.

260 AVERT's observation window. See http://www.avert.org accessed 07 June 2019. See also https://www.hiv.gov/federal-response/funding/budget accessed 26 April 2019.

diverse factors, the common denominator is the cost of ARVs, which remains a barrier inhibiting or limiting their access to treatment.[261]

The key question for the purpose of this chapter is premised on reasons for the high cost of HIV treatment in the form of ARVs. The high cost of ARVs is primarily ascribed to IPR that emanate from the development and manufacturing of the ARVs.[262] This question is a burning issue for PLWH and relates to whether a patent-holder's rights to his or her intellectual property through patent law should supersede or override the right to access health care services of PLWH, which would include the affordability of ARVs for those living with HIV. [263] This thesis argues that there should be a balance between the patent holder's competing rights and those of the patient's access health care services.[264] This access should be achieved without undue financial burden to a patient,[265] yet also not undermine the rights a patent-holder whose time and financial investment in the manufacturing process of the ARVs should not be negated. [266]

During the currency of an initial patent, the formulation and manufacturing process of the final product remains protected and accentuated through the licensing of the patented drug, thus negatively influencing the manufacturing of generic ARVs. Without patent protection, generic drugs could be available in the marketplace upon expiration of the exclusivity period.[267] Meanwhile, Cook[268] propounds that, as it is typical in the initial ARV manufacturing structure, the profiled pharmacological activity of a drug's design in whatever structural change warrants an IPR. Hence, it is necessary to determine the effect of the IPR system on patients' access to ARVs and the affordability of ARVs, which in turn, prompts the question whether the right of access to health care services is impeded by the IPR system.

---

261 Yethi Dlamini, 'Shortage of ARVs spark infection fears' (The Star 5 June 2019) https://www.pressreader.com/south-africa/the-star-south-africa-late-edition/20190605/281522227582607 accessed 26 May 2019.

262 Abusive patenting practices by pharmaceutical companies, and inflated HIV related drug prices negatively affected access to treatment. https://www.msf.org/south-africa-country-takes-landmark-step-access-medicines accessed 10 May 2019.

263 Access Challenges for HIV Treatment Among People Living with HIV and Key Populations in Middle-Income Countries, (Policy Brief October 2013) 1. See also Pharmaceutical Manufacturer Association of SA and Another: In Re Ex Parte President of the Republic of South Africa 2000 (2) SA 674 (CC).

264 World Health Organisation 'The World Health Report – health systems financing: the path to universal coverage" World Health Organization' (WHO 2010) http://www.who.int/iris/handle/10665/70496 accessed 31 May 2019.

265 PN Bennett and MJ Brown, *Clinical Pharmacology* (9 edn McGraw-Hill Medical 2003)135. Richard Murphy, *et al,* Coadministration of Lopinavir/Ritonavir and Rifampicin in HIV and Tuberculosis Co-Infected Adults in South Africa (2012) 7(9) Public Library of Science.

266 Article 31(h) of the TRIPS Agreement refers to "adequate remuneration" of the patent-holder.

267 Patents and the quality, safety and efficacy of medicines. Jama Editorial (2015) 105(11) 905-915.

268 Cook T, *A user's Guide to Patents* (2 edn Tottel Publishers 2008) 331.

The UNAIDS estimated that at the end of 2018, there were nearly 36.7 million PLWH, while slightly less than half - about 18.2 million people - were receiving ART.[269] Projections by the South African National AIDS Council (SANAC) indicate that the number of people receiving HIV treatment has more than doubled between 2010 and 2018.[270] Although everyone infected with the virus has a right of access to health care services, the high number of 18.5 million PLWH not falling within the treatment bracket, is a cause for concern. As stated above, the effect of the protection of IP *vis-a-vis* access of patients to ARVs is worth examining, although it has been contested that patent protection is not the only impediment to ARV access. [271]

This chapter also examines the effect of economic considerations, as well as the legal protection of patents on the right to access health care services for PLWH in South Africa. Relevant to this issue is the impact of ongoing commitment globally by WHO and its partners to combat the epidemic of HIV/AIDS through initiatives, which either provide or support ART, including the express expansion of access to treatment in LMICs across the world.[272] The WHO and UNAIDS imposed a global obligation on LMICs to participate in the requirements of the existing international instruments on IPR laws in a quest to curb the pandemic through national and international strategies and policies.[273] In response to this obligation, which in South Africa's case, culminated in Court, the South African National Department of Health sought a Constitutional

269 UNAIDS Data 2018, https://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf accessed 31 May 2019.

270 Ashleigh Furlong, 'HIV treatment programme doing well but long way to go' (GroundUp 26 June 2018) https://www.groundup.org.za/article/hiv-treatment-programme-doing-well-long-way-go/ accessed 02 June 2019.

271 Omar Gassama and Chien-Huei Kao, 'Factors Associated with Adherence to Antiretroviral Therapy among HIVI infected Adults in the Gambia' (2018) 9(771) Journal of AIDS & Clinical Research. Reports that there are notable glitches created by the patenting of medicines. Galloway G. Parliamentary Reporter Ottawa. Attaran and Gillepsie maintain that patents and patent law are not a major barrier to treatment access in and of themselves, but conclude that a variety of de facto barriers are more responsible for impeding access to antiretroviral treatment, including but not limited to the poverty of African countries, the high cost of antiretroviral treatment, national regulatory requirements for medicines, tariffs and sales taxes, and, above all, a lack of sufficient international financial aid to fund antiretroviral treatment(Jama 17 October 2001) 286(15) 1890.

272 World Trade Organization Report.,' Supporting access to treatment in developing countries across the world' (WTO 18 July 2012, updated 30 April 2018) https://www.wto.org/english/res_e/publications_e/world_trade_report18_e.pdf accessed 15 June 2019.

273 'Annotated Agenda' (UNAIDS 26 September 2018) https://www.unaids.org/sites/default/files/media_asset/20181211_UNAIDS_PCB43_Agenda_EN.pdf accessed 17 March 2019. See also 'the South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022' https://www.gov.za/sites/default/files/gcis_document/201705/nsp-hiv-tb-stia.pdf accessed 17 March 2019.

Court order to endorse the inclusion of section 15C into the MRSA[274] to address gaps relating to access to ARVs.

This chapter also provides further details concerning Section 15C,[275] which stipulates processes that ensure the supply of medicines at more affordable cost, which has a direct bearing on the discrepancy in respect of affordability of the ARVs to PLWH. According to the South African National Aids Council (SANAC) the fourth National Strategic Plan (NSP) for HIV, tuberculosis and sexually transmitted infections was issued in 2017. This five-year plan (2017–2022) aims to fast-track the progress towards access and affordability of drugs and to transition these epidemics from being a public health threat by the year 2030. The previous NSP of 2012–2016 saw a reduction in infections but could not affirm accessibility and affordability of drugs to public patients.[276]

The WHO and UNAIDS underscore the importance of international instruments relevant to intellectual property rights to be sensitive towards the right to access health care services in general, which would include access to and affordability of ARVs, supported by the UNAIDS strategy to integrate access and availability into the front-line services for PLWH.[277] As can be expected, this was followed by an assessment of the prospects, benefits and challenges of *sui generis* IPR protection and the introduction of patents, licences, and their effect on the market and non-reciprocal access for ARVs. [278]

As stated above, this chapter also briefly considers the economic effect of international markets in relation to the right of access to health care services of PLWH in LMICs.[279]

---

274 Medicines and Related Substances Act 101 of 1965, 15C inserted by Section 10 of Act 90 of 1997.

275 Section 15C provides that the government is geared to take measures to ensure a supply of more affordable medicines and to prescribe conditions for the supply in certain circumstances to protect public patients, notwithstanding anything to the contrary contained in the Patents Act 57 of 1978.

276 South Africa J HIV Med. 2018; 19(1): 796. See also, Kathryn Hopkins, Tanya Doherty and Glenda Gray, 'Will the current National Strategic Plan enable South Africa to end AIDS, Tuberculosis and Sexually Transmitted Infections by 2022?' (2018) 19(1) South African Journal of HIV Medicine 796.

277 UNAIDS' Fast Track targets for 2020 include: 90% of people living with HIV know their status; of whom 90% are on treatment; of whom 90% are virally suppressed (90-90-90) https://www.avert.org/global-hiv-targets accessed 17 March 2019.

278 In developed countries, the introduction of highly active antiretroviral treatment (HAART) and the availability of drugs for opportunistic infections and malignancies (PCP, cytomegalovirus disease, herpes, tuberculosis) led to a substantial reduction in AIDS mortality. In MICs, however, access to these drugs is seriously lacking. See Patent situation of HIV/AIDS-related drugs in 80 countries Geneva, January 2000. A joint publication of UNAIDS and WHO. See https://www.who.int/3by5/en/patentshivdrugs.pdf accessed 04 June 2019.

279 L Lessig, *The future of ideas The Fate Of The Commons In A Connected World* (Random House New York 2001) 259. With respect to patents, Professor Lessig similarly states that patents are

The relevant discussion concerning international IPR instruments is justified and necessitated by reference to Section 39(1) of the South African Constitution, which provides that: "[W]hen interpreting the Bill of Rights, a court, tribunal or forum - (a) must promote the values that underlie an open and democratic society based on human dignity, equality and freedom; (b) must consider international law; and (c) may consider foreign law."

From this Constitutional obligation, it is then axiomatic that the right to access health care services, entrenched in the Bill of Rights, should be examined by reference to the relevant international legal framework.

The instruments' provisions will be reviewed to establish whether they align with the right of access to health care services and their role in influencing the affordability of ARVs in LMICs will be traced.[280]

The next section briefly outlines the origin and role of patents, followed by a critical analysis of the relevant international instruments. In the final instance, the South African approach to TRIPS and other IP related international instruments will be addressed.[281]

3.1.1 Brief overview on the origin and role of patents

The concept of patents[282] dates back to 600 BC.[283] As far back as 500 BC, a practice existed in terms of which chefs in Sybaris had the option to have up to a year of profit on a unique dish that they created. This could very well be the first known reference of intellectual property protection.[284] The first Industrial Revolution of the 18th century which began in the United Kingdom sparked the shift from manual home productions to machine-based manufacturing that took place in factories.[285] From the United Kingdom, the industrial boom spread throughout Europe and brought about a

---

not evil per se, but are so "if they do no social good." He explains that patents do no social good …"if they benefit certain companies at the expense of innovation generally."

280 The National Strategic Plan 2017-2022 of South Africa records the country's impecuniosity in the Foreword.

281 These instruments address eight specific health issues— infectious disease control, food safety, tobacco, environment, access to drugs, health services, food security as well some emerging issues, such as biotechnology and, in each case, examples of challenges and opportunities in implementing coherent trade and health policies are provided.

282 https://www.ucl.ac.uk/laws/people/sir-robin-jacob accessed 18 May 2019.

283 The patent in question was for "some kind of new-fangled loaf of bread" which had an economic value to the baker. https://www.upcounsel.com/history-of-patents accessed 28 April 2019.

284 The guild system in the Middle Ages is believed to be the protection of intellectual property through the use of patents. https://www.upcounsel.com/history-of-patents accessed 28 April 2019.

285 In the 1700s, a series of innovations led to ever-increasing productivity, while requiring less human energy. https://www.history.com/topics/industrial-revolution/industrial-revolution accessed 28 April 2019.

significant amount of technology and knowledge transfer through borrowing, copying and modelling.[286] The English patent system was the crucial legal foundation upon which the Industrial Revolution could flourish.[287] As the patent system caught the attention of the European countries, the German organic chemistry artificial dye revolution became a turning point in the history of the pharmaceutical industry. Many of the products that the aniline dye factories produced had dual uses, both for the private civilian economy and for the military. Besides dyestuffs, products for civilian use included cosmetics, fertilizers, pesticides, and medicines, as well as an increasing number of chemical products for the film and photo industries.[288] The 18th and 19th centuries are known for the flexible legal systems and supportive national and international policies concerning the protection of intellectual property rights at the time.[289]

The United Kingdom prompted investments through the development of research and in other countries and propagated the onset of research on drugs such as penicillin.[290] With such discoveries in the pharmaceutical industry, the United States, Western Europe and Japan became the forerunners in drug discovery and development.[291] The industrial revolution's spread created a shift for these countries, from being borrowers, copiers and modellers to being innovators, leading them to acquire the status of 'special and differential' developed countries. The history of the development of patents is closely connected to the notion of economic power that is geographic in nature, thus creating a disparity between producing countries and recipient countries.[292]

Developments in the field of biotechnology have ushered-in new patents, including the patenting of pharmaceutical products.[293] With regard to the development of ARVs, the relevant patents relate to innovations, inventions, and discoveries of compounds to

---

286 B Kiliç, *Boosting Pharmaceutical Innovation in the Post-TRIPS Era- Real-Life Lessons for the Developing World* (Edward Elgar Publishing Limited 2014) 1.

287 C MacLeod, *Inventing the industrial revolution: the English patent system,* (Cambridge University Press 1988) 1660-1800.

288 http://www.wollheim-memorial.de/en/entstehung_der_deutschen_farbenindustrie accessed 28 May 2019.

289 https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics accessed 21 September 2018.

290 A Flemming, B Chain and HW Florey, 'The global resource for scientific evidence in animal Research' for https://www.sciencehistory.org/historical-profile/howard-walter-florey-and-ernst accessed 28 April 2019.

291 Industrialisation spread to Belgium, France, Germany and the United States of America. https://www.history.com/topics/industrial-revolution/industrial-revolution accessed 28 April 2019.

292 MJ Trebilcock, *Advanced Introduction to International Trade Law* (Edward Elgar publishing 2015) 192.

293 G Gey, 'Timeline of Medical Biotechnology' https://www.biotechnology.amgen.com/timeline.html accessed 18 May 2019.

new medicines as essential health care and life sustaining products.[294] The expansion of the global market for ARVs has necessitated protection of the IPR through patents and registration of patents. [295] As alluded to above, a balance should be maintained between the protection of patents and the right of access to health care services. States have a legal obligation to promote access to health care services, which include addressing the underlying determinants of health, as intimated in the following statement by the WHO:

> "[U]nderstanding health as a human right creates a legal obligation on states to ensure access to timely, acceptable, and affordable health care of appropriate quality as well as to providing for the underlying determinants of health, such as safe and potable water, sanitation, food, housing, health-related information and education, and gender equality''.[296]

When discussing access to ARVs, the rights-based approach's significance is demonstrated by the participation of all stakeholders, particularly when, in the case of countries, they subscribe to international instruments that influence national legislation and policymakers.

The tension between the competing or opposing interests of patent protection vis-à-view the right of access to health care services (and ARVs) is pivoted on a determination of the extent of interests and relevance for society at a given point in time; for example, trade or public health. [297] An assessment of the opposing interests will inevitably need to satisfy the proportionality test in this regard. [298]

3.2 International economic instruments relating to intellectual property rights and their impact on HIV treatment

South Africa is a Member State and signatory to most of the United Nation's treaties, and therefore, bound by the provisions of the treaties by virtue of Section 39(1)(b) of the Constitution of the country, which mandates the Courts, when interpreting the Bill

---

294 The National Institution of Allergy and Infectious Diseases supports basic research to identify novel strategies to prevent HIV from taking hold and replicating in the body, as well as preclinical research to formulate antiretroviral drugs that can be tested in people. https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development accessed 27 May 2019.

295 Patent law, as it exists today, is traceable to 15th century Venice, where the first patent law was created and enforced, preventing others from using the inventions of inventors without proper permission or authority. https://patent.laws.com/patent-law-history accessed 10 May 2019.

296 World Health Organization 'Human rights and health' (WHO 29 December 2017) https://www.who.int/news-room/fact-sheets/detail/human-rights-and-health accessed 17 July 2019.

297 Article XX of GATT provides for the interests that may justify adopting restrictive measures of freedom of expression and of free trade respectively. https://www.wto.org/english/res_e/booksp_e/gatt_ai_e/art20_e.pdf accessed 17 July 2019.

298 EB Rodrigues, *The general exception clauses of the TRIPS Agreement* (2012, United Kingdom Cambridge University Press 2012) 53.

of Rights, to consider international law. In Section 231(4) of the Constitution, international law includes international agreements that have been enacted into national legislation, or an agreement's self-executing provision approved by parliament, unless such provision is inconsistent with the Constitution or an Act of Parliament. Furthermore, Section 233 of the Constitution determines that "when interpreting any legislation, every Court should opt for any reasonable interpretation of the legislation that is consistent with international law over any alternative interpretation that is inconsistent with international law". [299]

It is then necessary to further consider the context and background of relevant IP-related international instruments; the purpose of the specific clauses in the instruments in relation to patenting of medicines, as well as the provisions that have a bearing on the pricing of ARVs. Accordingly, the following key organisations and international economic IPR instruments are highlighted below: The General Agreement on Tariffs and Trade (GATT); General Agreement on Trade in Services (GATS); the WTO and TRIPS; the Doha Declaration; the World Intellectual Property Organisation (WIPO); the WHO, the Organisation for Economic Co-operation and Development (OECD) and the Global Fund support the patenting of HIV drugs.

3.2.1 The General Agreement on Tariffs and Trade (GATT)

The GATT is an original international trade treaty, an organisation of 128 countries founded in 1947, which steadily evolved to become the WTO with 159 members.[300] In 1994, GATT made express reference to IPR and sought to provide barriers where necessary for the protection of international trade in goods, which included custom duties, subsidies and imports on health related trade.[301] GATT, through Article XI:I discourages parallel imports, thereby encouraging the adoption of an international regime on exhaustion. As far back as 1989, Paul Samuelson and William Nordhaus noted the basic underlying principles of trade and IPR protection.

Parallel importation (often known as grey marketing) [302] means the import of a product (such as a pharmaceutical produce) protected as a patent is 'parallel' to a domestic intellectual property (IP) right in the country of importation.[303] Furthermore, parallel imports and international trade parallel importation apply in the case of an item or

299 Constitution of the Republic of South Africa, 1996.
300 http://capping.slis.ualberta.ca/global/sandra/history.html accessed 30 January 2019.
301 https://www.wto.org/english/res_e/booksp_e/gatt_ai_e/art20_e.pdf 30 January 2019.
302 Paul Samuels and William Nordhaus, *Economics* (13 edn McGraw Hill 1989) 867-910.
303 S Gervais and S Frankel 'International Intellectual Property Rules and Parallel Importing' (2016) Research Handbook on Exhaustion and Parallel Imports 85-105.

commodity that is legitimately marketed under the IP framework in a certain country is imported into another country by means of an unofficial trade mechanism against the interests of the applicable rights holder in the other (second) country. Such importation is permissible in the event of the goods being produced with the consent of the original patent-holder for subsequent sale without a clear notice of restriction.

From the perspective of Matsushita *et al.*, [304] parallel importation is the concept used for the importation and resale of genuine products from a distributor who legally obtained such products from a manufacturer at a low price, instead of buying directly from the manufacturer. Exhaustion of rights or "first sale doctrine", on the other hand, refers to the notion of IP rights being exhausted after the sale of the product by the IP owner or with his/ her consent anywhere in the world.[305]

The sale of original HIV medicine both domestically and abroad is influenced by the disparity between the notions of "most favoured nations" principle (MFN) and "national treatment principle" (NTP). The most-favoured-nation (MFN) principle, expressed in Article I:1 of GATT, means that a country should grant some privileges related in a trade agreement to any of the WTO's member nations, and that if any privileges are granted to any member nation by another member nation of the WTO, then the same privilege of "like" products has to be granted to all the other member nations of the WTO. The underlying aim of the MFN is to promote trade and provide equal opportunity to get the best benefits of any member nation's resources.[306]

The MFN principle could be misleading in the sense that it seeks to promote equal treatment and not any form of preferential treatment to one nation specifically. In other words, the granting of MFN status to a country implies that the tariff rates for that partner will not be any higher or lower than any other country for which the trading partner has given the same status. This means that the best trade practice offered by one trading partner will be enjoyed by all the nations which have been granted this status. Hence, despite levelling the playing ground by providing equal commercial

---

304 Matsushita, *et al*, *The World Trade Organization: Law, Practice and Policy* (2 edn Oxford International Law Library 2006) 702.

305 Lorie, Graham and Stephen, 'Intellectual Property's First Sale Doctrine and the Policy Against Restraints on Alienation' (2020) 7(3) 7 Tex. A&M Law Review 497.

306 D Rai 'Non-Discrimination Principle: MFN and National Treatment in the GATT' (IPleaders 1994) http://www.blog.ipleaders.in/non-discrimination-principle-most-favoured-nation-mfn-and-national-treatment-in-the-general-agreement-on-tariffs-and-trade-gatt-1994/. accessed 23 September 2021.

opportunities, this tends to benefit economically stronger countries over developing nations, for several reasons not relevant for this discussion.[307]

In accordance with Article III of GATT, the national treatment principle prohibits any of the member nations from favouring or giving any advantages or raising any benefits to their domestic products or goods over imported products of other member nations. In the South African litigation against compulsory licensing—discussed in more detail below—GATT's involvement in "removing barriers" was conspicuous for its contradiction in that GATT was hardly transparent. The legal conflict between South Africa and the United States arose in 1997 when the latter threatened trade sanctions against South Africa unless the country repealed a section of the Medicines and Related Substances Control Amendment Act, which permitted parallel importing and compulsory licensing.[308]

Compulsory licensing refers to a flexibility in the sphere of patent protection incorporated in TRIPS, and in terms of which a country allows another country or entity to produce a patented product or process without the patent owner's consent, or when the said country plans to use the patent-protected invention itself. At the time, South Africa's policy towards medical products was challenged, as the Minister of Health previously had the discretion to set aside any domestic or international patent obligations which were regarded as impeding upon the health and welfare of South Africans.[309] Based on the latter, the South African government was able to expand the scope for compulsory licensing and parallel imports of medicines in the country beyond the limitations imposed by TRIPS in this regard.

Consonant with the purpose of this chapter regarding HIV treatment, GATT has to act as a forum for trade issues regarding ARVs since the organisation has the ability to render judgments in trade disputes. However, it could not enforce those decisions.[310] Parallel importation, referred to in the introduction of this section and built on the principles of exhaustion of IPR, presented problems for South Africa at the time, because they are based on three competing principles of exhaustion of IPR, which are the universal or international exhaustion principle, the domestic or territorial exhaustion

---

307 'Most Favoured Nation And National Treatment' https://phdessay.com/most-favoured-nation-and-national-treatment/ accessed 23 September 2021.

308 Section 15C of the Medicines and Related Substance Control Amendment Act 90 of 1997. https://www.wilsoncenter.org/chapter-2-americas-trade-agreements accessed 28 May 2019.

309 'The South Africa dossier on the Consumer Project on Technology internet pages' http://www.cptech.org/ip/health/sa/ accessed 23 September 2021.

310 E Reinhardt, 'Adjudication without Enforcement in GATT Disputes' (2005) 45(2) Journal of Conflict Resolution 174-195.

principle and the regional exhaustion principle.[311] The universal or international exhaustion principle provides that an IPR owner's rights become exhausted upon the first sale of the goods anywhere in the world.[312]

Consequently, South Africa upheld the view that parallel import is an issue that should be left to the discretion of individual WTO Member States. The international pressure to lower the prices for AIDS medicines in developing countries, increased. Pressure came from AIDS activists, people living with HIV/AIDS, generic pharmaceutical companies, and non-governmental organisations (including Médecins Sans Frontières, Consumer Project on Technology, ACT-UP, and the Treatment Action Campaign). Activists and world leaders, including Nelson Mandela, drew global media attention to this issue in their opposition to the lawsuit brought (and eventually withdrawn) by 39 drug manufacturers against the South African government's Medicines and Related Substances Act of 1997, which sought to expand access to low-cost AIDS medicines through various measures.[313]

The prevailing and deteriorating health condition of South Africans living with HIV and AIDS compelled the government to take a stance in opposing parallel importation. South Africa defended its stance against a relevant clause in the agreement which provided that the country against which judgment is given, has to agree to the sanction prescribed by the judgment.[314] As one of the three power-wielding pillars that facilitate agreements in the expansion of world trade,[315] GATT did not live up to its mandate expectations to effectively prevent any international sanctions to a country that is allegedly accused of bargaining in bad faith. South Africa (which stood accused) withdrew from the negotiated agreement in respect of its own subjects' immediate health care needs.[316] It is through successive negotiation rounds that GATT responded

311 Nguyen Nhu Quynh, 'Parallel Trade of Patented Pharmaceuticals: A Discussion from Developing Country Perspective' (Ministry of Science and Technology 2014) http://iprenforcement.most.gov.vn/cac-bai-nghien-cuu-shtt/parallel-trade-of-patented-pharmaceuticals-a-discussion-from-developing-country-perspective accessed 19 July 2019.

312 E Reinhardt, 'Adjudication without Enforcement in GATT Disputes' (2005) 45(2) Journal of Conflict Resolution 174-195.

313 Reich and Bery, 'Expanding Global Access to ARVs: The Challenges of Prices and Patents' (2005) New York Academic Press 328-329..

314 World Trade Organization 'Article XXI Security Exceptions' (WTO 01 January 2016) https://www.wto.org/english/res_e/booksp_e/gatt_ai_e/art21_e.pdf accessed 09 July 2019.

315 The GATT as a multilateral agreement set the legal ground-rules for international trade. https://courses.lumenlearning.com/boundless-business/chapter/international-trade-agreements-and-organizations/ accessed 09 July 2019.

316 The activist pressure helped place the issue of access to AIDS medicines high on the international health agenda and onto the policy agenda of the United Nations and the G-7 countries in the last years of the twentieth century. HIV is a virus spread through certain body fluids that attacks the body's immune system, specifically the CD4+T cells, often called T cells. https://www.wto.org/english/res_e/booksp_e/gatt_ai_e/art20_e.pdf 30 January 2019.

to the pressure, and in the process facilitated a huge reduction in world trade impediments, which culminated in the advent of GATS.

3.2.2 The General Agreement on Trade Services (GATS)

The General Agreement on Trade Services (GATS), a WTO agreement and conducted within the framework of GATT, was operational on January 1, 1995 as a new multi-lateral trade instrument, emanating from the Uruguay Round Negotiation (URN).[317] One of the other major results of the URN was the implementation of inter-country health services.[318] The GATS provides legally enforceable rules covering all international trade services and investment in the service sector, which includes health related services.

To understand the concern about the overlap between GATS and international health policy, it is necessary to have some understanding of its context in world trade and its mandate to manage and enforce side-agreements liberally without sacrificing national sovereignty.[319] Drager and Fidler[320] opine that any liberalisation under GATS should aim to produce health-related services of better quality, and affordable and effective for greater equity in health outcomes.[321]

According to GATS provisions, members are not required to commit to national treatment,[322] but when they do make market access commitments relevant to a specific sector, they should record and schedule all issues of national treatment that a country wishes to maintain.[323] In its preamble, GATS refers to the recognition of members' right to usher-in new regulations in their own territories, including the ability of a country to supply services within their own borders for the purpose of achieving

---

317 GATS is a landmark achievement of the Uruguay Round, whose results entered into force in January 1995. https://www.wto.org/english/info_e/site2_e.htm accessed 09 July 2019.

318 GATS promotes domestic services by expanding these to international platforms. Ryan Wenger, *et al, Core Curriculum for Primary Care Pediatric Nurse Practitioners* (Mosby 2006) 154.

319 The overlap is significant, making GATS an important treaty in terms of its potential effect on health policy. Chapter 5 on "Scope of GATS and Health Policy" examines these issues.

320 Richard Smith, *et al, A Handbook of International Trade in Services* (Oxford University Press 2008) 437. Fidler elucidates from both the trade and health perspectives the nature and implications of international trade in the health sector, and thus it assists the formulation of trade policy and international negotiations in the health sector.

321 The World Health Assembly (WHA) Resolution 59.26. on International trade and health. See also the World Health Organization report on Trade, foreign policy, diplomacy and health. https://www.who.int/trade/trade_and_health/en/ accessed 19 July 2019.

322 GATS 'Agreement on National Treatment' (Article XVII) https://www.wto.org/english/res_e/publications_e/ai17_e/gats_art17_jur.pdf accessed 09 July 2019.

323 Gilles Muller, *Troubled Relationships Under the GATS: Tensions between Market Access (Article XVI, National Treatment (Article XVII) and Domestic Regulations (Article VI)* (Cambridge University press 2017).

police objectives, while also fulfilling national needs.[324] Given the disproportionate degree of development of services that persist in different countries, the particular needs of LMICs is to exercise their right to health services by insisting on trade negotiations with developed countries. Like the GATT, this agreement focused on reducing barriers to international trade, while also emphasising the trade of services relating to health issues; hence, liberating LMICs from the enforcement of patent rights on ARVs.[325] In this regard, Article II:1 of GATS states as follows:

> "With respect to any measure covered by this Agreement, each Member shall accord immediately and unconditionally to services and service suppliers of any other Member treatment no less favourable than that it accords to like services and service suppliers of any other country".[326]

The GATS offers certain exceptions to their rules in that it authorises Members in specified circumstances to introduce and to maintain measures in contravention of their obligations under the Agreement, including the MFN requirement or specific commitments.[327] The relevant Article[328] provides cover for, *inter alia*, measures necessary to protect public morals or maintain public order, and human, animal or plant life and health.

Examples of the suggested permissible services provided at non-market conditions include health, education, and the social security schemes. This would include promotion of ARV access and related health services, as part of a broad and comprehensive approach. Notwithstanding, GATS proposes that WTO members be forced to privatise public health and health care services currently provided by governments,[329] since HIV care and drug costs dominate health expenditure.

The GATS critics[330] worry that the duty to liberalise trade in services between Member States is progressive and if misconstrued, will eventually jeopardise the recipients of

---

324 GATS item 1.1 WTO ANALYTICAL INDEX GATS – Preamble' (Jurisprudence December 2018) https://www.wto.org/english/res_e/publications_e/ai17_e/gats_preamble_jur.pdf accessed 09 July 2019.

325 GATS and health related services (World Health Organisation) https://www.who.int/trade/resource/foldout/en/ accessed 09 July 2019.

326 Legal Review of the General Agreement on Trade in Services (GATS) from a Health Policy Perspective Prepared by The Gats Legal Review Team for The World Health Organization.

327 C Joy and P Hardstaff, 'Whose Development agenda? A Preliminary Analysis of the 109 EU GATS Requests' (2003) 29 World Development Movement.

328 World Trade Organization 'ANALYTICAL INDEX GATS – Article XIV (Jurisprudence)' (WTO December 2018) https://www.wto.org/english/res_e/publications_e/ai17_e/gats_art14_jur.pdf accessed 15 June 2019.

329 C Joy and P Hardstaff, 'Whose Development agenda? A Preliminary Analysis of the 109 EU GATS Requests' (2003) 29 World Development Movement.

330 R Chanda in DESA Discussion Papers which are preliminary documents circulated in a limited number of copies that stimulate discussions and comments on GATS. http://www.un.org/esa/papers.htm accessed 21 June 2016.

services. For countries in which the private sector plays little or no role in the provision of public health and health care services, the proposed privatisation of public services would constitute a radical structural transformation on how such countries pursue their health policy. GATS' proposal might "lock in" such structural changes by preventing WTO members from reversing policy experiments with privatisation in the health sector.[331] A legal review of the GATS points out that the system of settling disputes by the WTO (discussed below) also affects the structure of the provision of health-related services, because it effectively allows foreign corporations, through their home governments, to challenge domestic regulation of health-related services in another country, as seen in the South African case.[332]

3.2.3 The WTO and TRIPS Agreement

In 1986, GATT began the Uruguay Round Negotiations that lasted until 1994, paving the way for the WTO's formation in 1995.[333] However, the WTO collaborates with the WHO in matters relating to health trade through GATS, while the WTO portrays a better deal in relation to health trade, in hindsight, the WTO enabled the TRIPS agreement.[334] The latter Agreement presents a conundrum in that Article 27.1 of the Agreement limits trade agreements on drugs by emphasising that "[…] patents shall be available and patent rights enjoyable without discrimination as to the place of invention."[335]

The most significant reform initiated by the TRIPS Agreement was its Article 27.1 demand in Article 27.1 for member countries to grant pharmaceutical product patents, thereby bringing intellectual property governance under the WTO's fiat. Accordingly, countries were obliged to increase the protection and treatment of pharmaceutical products in the same manner as they did for other products. Prior to the TRIPS

---

331 Gould and Joy 2000: 8-9; Howse and Tuerk 2002: 5; Sinclair and Grieshaber-Otto 2002: 75-76; Joy and Hardstaff 2003: 30; Joint Submission to the World Health Assembly (2003) Chapter 3.

332 D Fidler, CM Correa and O Aginam, 'Legal review of the General Agreement on Trade in Services (GATS) from a Health Policy Perspective' (World Health Organization, January 2006) https://www.researchgate.net/publication/238743323_Legal_Review_of_the_General_Agreement_onTrade_in_Services_GATS_from_a_Health_Policy_Perspective accessed 24 June 2019.

333 Martin Daunton, Amrita Narlikar and Robert Stern, *The Oxford Handbook on The World Trade Organization* (Oxford University Press 2012).

334 Chomsky N. Avers that WTO intends to cut back innovation, growth, and development and to maintain extremely high profits for patent holders. See Global Issues Social, Political, Economic and Environmental Issues That Affect Us All. http://www.globalissues.org/article/42/the-wto-and-free-trade#ChinasEntryintotheWTO accessed 24 June 2019.

335 TRIPS agreement means the agreement on Trade Related Aspects of Intellectual Property Rights. Article 21.1 introduces a derogatory term of discrimination. In interpreting article 21.1 of TRIPS Agreement the World Trade Organization Analytical Index avers that a discriminatory exception that takes away enjoyment of a patent right is discrimination as much as is discrimination in the basic rights themselves. https://www.wto.org/english/res_e/publications_e/ai17_e/trips_art27_jur.pdf accessed 03 June 2019.

Agreement, LMICs did not grant patents to pharmaceutical products.[336] The developing countries that already granted patents for medicines usually did not grant the required protection of these patents for the twenty-year minimum term stipulated by TRIPS.[337]

The objective of the TRIPS Agreement temporarily blocked the establishment of prospects towards innovative ideas to enhance values in the research and development of ARVs. The Agreement offered certain flexibilities as shown below:

- compulsory licensing and government use: the ability of the relevant authorities to grant and define when to issue a license to manufacture, use or sell a generic equivalent variant of a patented drug unless the patent holder has consented, and is compensated;
- exhaustion of patent rights: the ability to decide when patent holders lose the exclusive right over the re-sale of their products. This enables the importation of patented drugs from countries in which they are sold more cheaply (termed “parallel importation”);
- exceptions to patent rights: the ability to allow the manufacture and testing of a drug before the patent expires, in order to obtain regulatory approval for making a generic drug once the patent expires (termed “bolar provision”); and
- prohibition of anti-competitive practices: the ability to penalise pharmaceutical patent owners that abuse their dominant position in contractual relationships and engage in prohibitive pricing.

Whilst some WTO Agreements protected patent-holders, an objective which facilitated high drug prices, the WHO sought the elimination or reduction of import duties on drugs, vaccines or other medical supplies.[338] The key concern was that whilst the TRIPS Agreement promotes incentives for research and development into new drugs, the concern arose that it could lead to drug price increases due to more stringent patent right protection. The above notion created uneasiness among Member States.

Some problems relating to TRIPS that have been identified include, among others, the following:

---

336 KC Shadlen, ‘Patents and Pills, Power and Procedure: The North-South Politics of Public Health in the WTO’ (2004) 39(1) Studies in Comparative and International Development 83-84.

337 KC Shadlen, ‘Patents and Pills, Power and Procedure: The North-South Politics of Public Health in the WTO’ (2004) 39(1) Studies in Comparative and International Development 83-84.

338 M Everard*, Drugs and Money - Prices, Affordability and Cost Containment* (IOS Press 2003) 158.

- the aim of TRIPS is to classify Member States from developed countries to LDC (least developed countries) which is ironic, given that this would allow further competition and better prices for drugs and other products, which is something that transnational corporations hold as the benefits of free trade and corporate-led capitalism with minimal restrictions;[339]
- the effect of the 20-year period of a patent protection is to basically deny others (such as LMICs and their corporations) from developing alternatives that would be cheaper;[340]
- technology transfer is encouraged under Article 66.2; however, there are stringent measures and a reporting system that could easily discourage inventors, which again is a direct contradiction for those who support the WTO and free trade in its current forms;[341]
- TRIPS generally enables transnational corporations to grow more due to their profits made, while others tend to decline further; and
- while there are some provisions, i.e., compulsory licensing allowing the creation of alternatives in cases of emergency and parallel importing, TRIPS casts a negative effect on permits to shop around on international markets for the cheapest price of the same product. However, it is not far-reaching as many nations face pressure from countries such as the United States when they apply these measures, even though the USA relies on these measures themselves.

Thus far, the discussion in this chapter have shown that the TRIPS, the WTO and general international trade related agreements do not consider public health needs but promote commercial interests instead. [342] This position was exacerbated by the handling of trade disputes by the WTO.

Member States agreed that trade disputes shall be heard before a WTO panel and that its decisions would be binding.[343] The WTO appointed independent experts base

---

339 World Trade Organisation, 'Staff Working Paper ERSD-2018-01' (22 February 2018) https://www.wto.org/english/res_e/reser_e/ersd201801_e.pdf. accessed 30 August 2022.

340 https://www.wto.org/english/tratop_e/trips_e/factsheet_pharm02_e.htm. accessed 30 August 2022.

341 Suerie Moon 'Does TRIP Art 66.2 Encourage Technology Transfer to LDC' https://unctad.org/system/files/official-document/iprs_pb20092_en.pdf accessed 07 December 2022.

342 Anup Shah, 'The World Trade Organization and Free Trade' (WTO 02 July 2007) https://www.wto.org/english/res_e/publications_e/ai17_e/trips_art27_jur.pdf accessed 24 June 2019; WTO Agreements at the1986–94 Uruguay Round negotiations, signed at the Marrakesh ministerial meeting in April 1994.

343 Shah observes that the reality is far from the principle. Anup Shah, 'The World Trade Organization and Free Trade' (WTO 02 July 2007) https://www.wto.org/english/res_e/publications_e/ai17_e/trips_art27_jur.pdf accessed 24 June 2019.

their judgments on "interpretations of the agreements and individual countries' commitments".[344] Given the above dilemma involving the WTO and WHO in the context of patent protection on ARVs, round table discussions and conventions ensued, in an attempt to counter the decisions of the WTO's TRIPS Agreement on drugs related matters. The TRIPS Agreement was hence amended through the Protocol of 6 December 2005, which became effective on 23 January 2017.[345] The amendment inserted a new Article 31bis into the Agreement, as well as an Annexure and Appendix.[346] The latter two documents provide the legal basis for WTO members to grant special compulsory licences exclusively for producing and exporting affordable generic medicines to other Member States that cannot domestically produce the needed medicines in sufficient quantities for their patients.[347]

For some Member States, especially the LMICs, the WTO's introduction of the TRIPS Agreement primarily serves to advance international trade through patent law as a legal system to safeguard the economic and legal rights of any person who invents, discovers, originates, creates, designs or makes something of value, hence compromising and relegating the health needs of LMICs to the back burner.[348] These agreements are considered by some to provide patent-holders with a veneer of legality, allowing TRIPS to exert economic influence whilst retaining ruthless dominance over pharmaceutical trade.[349] In this regard, the TRIPS agreement may be seen to limit the economic and legal dimensions of the production procedures of ARVs, specifically in the context of LMICs.[350]

Another enigma created by the TRIPS Agreement's provision is the exclusion of patents relating to ARVs on the basis that such patents should relate to geographic innovations that extend to other countries by means of either co-registration, patent cooperation treaty, licence issuance or the FDA's approval through valuable exclusivity

---

344 One of the primary roles of GATT is to support the needs of developing countries. https://www.wto.org/english/thewto_e/thewto_e.htm accessed 03 June 2019.

345 Paragraph 1 of Article X of the Marrakesh Agreement Establishing the WTO. Member states agree to make health flexibility permanent. Report of the General Council WT/L/641 8 December 2005.

346 Annex Item 1(a) meaning of pharmaceutical products was expounded and (b) eligible importing member was explained.

347 World Trade Organization 'TRIPS Agreement' (WTO 23 January 2017) https://www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm accessed 10 July 2019.

348 The World Trade Organization TRIPS Agreement are applicable to member states. However, their power has impacted negatively on non-member states as far as pharmaceutical IPR is concerned. https://www.upcounsel.com/patent-system accessed 28 April 2019.

349 T Pogge, *World Poverty and Human Rights* (2 edn Cambridge UK Polity Press 2008). The TRIPS Agreement globalised a monopoly patent regime that, by suppressing generic competition, kept the prices of advanced ARVs much higher than the long run cost production.

350 Micheal Trebilcock, Middle Income Access to Justice (University of Toronto Press 2012) 144.

rights.[351] The FDA's powers are not geographically confined. The exclusivity period applies to a new chemical entity (NCE) used in a drug. As foreign companies invest research time and money in developing new drugs, it is important to keep in mind that both the relevant U.S. patent law and the applicable FDA law could affect the exclusivity period for that drug. It is the FDA that effectively decides which products will be allowed in the stream of commerce. It is this stranglehold on the market that causes so many countries and their pharmaceutical markets to feel such frustration.

By their nature, IPRs are territorial rights and can be acquired in the territory of the country having legislation regulation IPR. As a consequence, IPR acquired in one country cannot be enforced in another country.[352] However, patent rights can catapult into international territories, for example, a patent may attract "ever-greening" for the patent-holder.[353] Ever-greening can be described as a legal strategy acquired by the innovator companies to protect and recover high costs incurred by the innovator towards all or any minor modifications that are intentionally made to the patent to obtain multiple patents on the same drug.[354] Thus, although not a formal concept of patent law, it is rather a social strategy referring to multiple ways in which pharmaceutical patent owners utilise regulatory processes to extend their high-earning intellectual property rights, often through highly profitable drugs, as a result of sales volume or unit price.

The term of patents generally extends to twenty years from the application's filing, which may be extended. The various measures that patent holders take to extend the patent life on their patents, such as developing new drug combinations or new versions of the same drug, or by fusing two existing drugs together, may negatively impact on the issue of the cost of drugs. Combined with the practice of ever-greening, patent-holders may manage their IPR in perpetuity nationally and internationally, thus negatively influencing HIV medicines' costs.[355]

---

351 Article 31(f) of TRIPS Agreement Article 31(f) of TRIPS Agreement https://www.wto.org/english/docs_e/legal_e/27-trips_04c_e.htm accessed 25 June 2019.

352 KT Chacko, 'Trade Related Aspects of Intellectual Property Rights (TRIPS)' (New Delhi 16 November 2010) http://wtocentre.iift.ac.in/FAQ/english/TRIPS.pdf accessed 25 June 2019.

353 Arun Kumar and Arun Nanda 'Ever-greening in Pharmaceuticals: Strategies, Consequences and Provisions for Prevention in USA, EU, India and Other Countries' (SSRN 31 March 2020) https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3549405 accessed 04 April 2020.

354 https://www.wto.org/english/res_e/booksp_e/gatt_ai_e/art20_e.pdf 30 January 2019.

355 At a Mercosur (South America's Southern Common Market) summit, then South African President, Nelson Mandela, had spoken of the need to ensure that there is more fairness in the globalization of trade process. Gustav Schellack, *Pharmacology in Clinical Practice - Application Made Easy for Nurses and Allied Health Professionals* (2 edn Juta 2010). Mercosur is the world's fourth largest economic power, after the United States, European Union and Japan.

Authorities in North America and Europe approve most patents for HIV drugs, and therefore, the LMICs and MICs need to go through the long licensing process to gain FDA (Food and Drug Administration) or EMA (European Medicines Agency) approval.[356] In addition, the current depressed and tumultuous economies in countries dependent on funding from HICs have a further negative impact on the manner in which HICs are viewing, and in some cases revamping their development aid strategies.[357]

3.3 Effect of the TRIPS Agreement on the manufacturing of antiretrovirals in low- to middle-income countries

As indicated above, the TRIPS Agreement introduced in 1994 and confirmed by WTO in 1995, sought to reduce the discretionary powers of WTO Members in respect of key elements of their national IP regimes,[358] as well as by defining how products can be protected through patenting. While just reward for one's efforts is reasonable, politics and power influences from developed countries tend to affect how patent processes work and their negative impact inevitably falls on LMICs, including PLWH.[359]

The TRIPS requires WTO members, with the exception of least the developed countries, to adopt minimum standards of intellectual property protection, including at least 20 years of patent protection in all technological fields.[360] The WTO subsequently established specific measures to limit exclusive patent rights through TRIPS' flexibilities into the process to adhere to public health related issues and to bend to organised protests to patenting of pharmaceutical products.[361] The flexibilities' function is to allow countries to balance the minimum standards of intellectual property with public health needs.

---

356 Each year, the U.S. government spends billions of dollars to help people in the United States and countries around the world who are living with HIV/AIDS. Angelique McCall and Gene Quinn, 'The FDA process, patents and market exclusivity' (CPA Global Report 12 March 2017) https://msmgf.org/wpcontent/uploads/2015/09/Access_Challenges_for_HIV_treatment_KAPs.pdf accessed 13 September 2018.

357 'Progress Toward Transitioning to a Sustainable Response in Partner Countries' (2013) National Academies Press 453-600, 544.

358 'TRIPS Agreement Law and Legal Definition' https://definitions.uslegal.com/t/trips-agreement/ accessed 30 July 2019.

359 Dean Jamison, *Disease Control Priorities in developing Countrie* (Oxford University Press 2006).

360 World Trade Organization 'TRIPS Agreement' (WTO 23 January 2017) https://www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm accessed 10 July 2019.

361 Sell in The Global Upward Ratchet, Anticounterfeiting And Piracy Enforcement Efforts: The State of Play, maintains that proponents of an IP maximalist agenda, ever since the WTO TRIPS negotiations that ended in 1994, they have been using every opportunity to increase intellectual property protection and enforcement beyond TRIPS.

It is self-evident that the international patenting process is associated with significant costs. However, providing revenue to the patent owner's country, does not hold the same benefits to the destination country of the patented drugs.[362]

The discussion above contextualises the context for the conclusion that the TRIPS Agreement has globalised a monopoly patent regime which, through suppressing generic competition, has kept the prices for ARVs very high.[363] Monopolies held by patent holders discourage, impede, and delay the manufacture of generic medicines in many poorer countries through the provisions on data exclusivity and other restrictions.[364]

Many patent applications in South Africa originate from foreign pharmaceutical companies, which leads to a rise in patent numbers, which generally affects competition and price increases of drugs sold in South Africa.[365] For reasons outlined above, the TRIPS Agreement and its imposition – in view of its scope and impact - is often described as one of the largest human rights violations relating to access to health care in human history.[366]

The Doha Declaration is discussed below as a next step in considering how trade outcomes affect HIV patients' right to access health care services, including ARVs.[367]

3.4 TRIPS Agreement and the Doha Declaration

The conclusion drawn from the discussion on the TRIPS Agreement above is that it gives preference to protection of patents for new medical processes and pharmaceuticals, which fails to advance the right to health in the context of trade.

---

362 Thomas Pogge 'Access to Medicine' (2008) 1(2) Public Health Ethics 73–82. https://doi.org/10.1093/phe/phn023 accessed 26 February 2019. Pogge maintains that the United States' IP offensive has since been continued through a series of bilateral free-trade agreements that include additional "TRIPS-plus" provisions. The patent holders may extend their monopolies and they also discourage, impede, and delay the manufacture of generic medicines, through data exclusivity and though restrictions on and political pressures against the effective use of compulsory licenses.

363 'Implications of transmission with undetectable HIV viral load: lower limit for HIV transmission excluded from model' (I-base 30 October) http://www.i-based.info/htb-south/314 accessed on 01 September 2019.

364 JR Turner, *New drug development: An Introduction to Clinical Trials* (2 edn New York: Springer 2019) 225.

365 K Alcom confirms that South Africa needs to reduce drug costs because of the expansion of ARVs for PLWH. 'Prep Implant Could last Well Over a Year' (AidsMap 24 July 2019) https://www.aidsmap.com/bulletin/conference-news/ias-2019/24-july-2019 accessed 01 September 2019.

366 https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/31/adverse-effects-of-antiretroviral-agents accessed 17 October 2017.

367 World Trade Organization 'The Fourth Ministerial Conference' (WTO November 2001) https://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_e.htm accessed 01 September 2019.

The extent to which the TRIPS Agreement limits the economic and legal dimensions of a country's manufacturing of ARVs should be debated on the grounds of the constitutionalising of health-related trade.[368]

The year 2001 marks increased global criticism of the TRIPS Agreement, especially by LMICs regarding ART and concomitant pharmaceutical patents on HIV drugs, compelled WTO members to embark on another round of negotiations at Doha.[369] A further contributor to the acceleration of the review on TRIPS is United Nation's Millennium Declaration in the same year,[370] which set, among others, the goal to achieve universal access for HIV/AIDS treatment for all those needing it.[371] This was followed by the Doha Declaration on the TRIPS Agreement and Public Health, which was adopted by the WTO Ministerial Conference of 2001 in Doha on November 14, 2001.[372]

Paragraphs 4 to 6 of the Doha Declaration are viewed as pertinent in this chapter insofar as they show governments agreeing that:

> "4. The TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all. In this connection, we reaffirm the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.
>
> 5. Accordingly, and in the light of paragraph 4 above, while maintaining our commitments in the TRIPS Agreement, we recognize that these flexibilities include:
>
> (a) In applying the customary rules of interpretation of public international law, each provision of the TRIPS Agreement shall be read in the light of the object and purpose of the Agreement as expressed, in particular, in its objectives and principles.

---

368 BR Hawkins, 'Economic Constitutionalism and Policy Space in Complex Systems of Multi-Level Governance: The Case of Trade and Health' (University of York, 15 July 2018) https://pure.york.ac.uk/portal/en/publications/economic-constitutionalism-and-policy-space-in-complex-systems-of accessed 07 December 2022.

369 Carlos Correa, 'Implications Of The Doha Declaration on the TRIPS Agreements And Public Health' (World Health Organization June 2002) https://www.who.int/medicines/areas/policy/WHO_EDM_PAR_2002.3.pdf accessed 01 September 2019.

370 General Assembly 'United Nations Millennium Declaration Resolution' (United Nations 18 September 2000) https://www.un.org/en/development/desa/population/migration/generalassembly/docs/globalcompact/A_RES_55_2.pdf accessed 01 September 2019.

371 World Health Organization, 'Millennium Development Goals (Goal 6, Target 2 B)' (WHO 19 February 2018) https://www.who.int/news-room/fact-sheets/detail/millennium-development-goals-(mdgs) accessed 01 September 2019.

372 World Trade Organization.' 'Declaration on the TRIPS agreement and public health' (WHO 14 November 2001 https://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm 06 September 2021.

(b) Each Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted.

(c) Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

(d) The effect of the provisions in the TRIPS Agreement that are relevant to the exhaustion of intellectual property rights is to leave each Member free to establish its own regime for such exhaustion without challenge, subject to the MFN and national treatment provisions of Articles 3 and 4.

6. We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002."

The effect of these provisions in the Declaration was that it allowed governments to provide compulsory licences on medical patents, or opt for alternative steps for protecting the health of the public. [373]

Then, in 2005, members of the WTO agreed to amend the TRIPS Agreement to make permanent the temporary waiver contained a WTO Decision of 30 August 2003, which itself fulfilled the requirement of Paragraph 6 of the Doha Declaration. This enabled a WTO member to provide compulsory licences for the export of generic variants of patented medicines to countries with insufficient or no manufacturing capacity in their pharmaceutical sector. The 2005 Ministerial Declaration states:

"We reaffirm the importance we attach to the General Council Decision of 30 August 2003 on the Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, and to an amendment to the TRIPS Agreement replacing its provisions. In this regard, we welcome the work that has taken place in the Council for TRIPS and the Decision of the General Council of 6 December 2005 on an Amendment of the TRIPS Agreement."[374]

Many extensions followed in order to reach the two-third threshold for ratifying the amendment, which finally happened in 2017, bringing the above TRIPS amendment into effect. The Doha Declaration, although praised by many public health officials for prioritising public health over intellectual property rights, access to ARVs is still hampered by other problems in LMICs, which include lack of resources and infrastructure.

---

373 World Health Organization observed that concerns had been growing that patent rules restrict access to affordable medicines for populations in developing countries in their efforts to control diseases of public health importance, including HIV, tuberculosis and malaria.

374 World Trade Organization, 'Ministerial Declaration' (WTO 18 December 2005) https://www.wto.org/english/thewto_e/minist_e/min05_e/final_text_e.htm#public_health 06 September 2021.

For Attaran and Gillespie,[375] despite the flexibilities introduced by the Doha Declaration, access to treatment for many African countries is impeded in many ways, for example, by insufficient finances to purchase relatively costly antiretroviral drugs; lack of political will among countries; poor medical care and infrastructure; inefficient drug regulatory procedures that exclude competing products from the marketplace, and high tariffs and sales taxes.[376] LMICs with high or growing HIV prevalence could therefore still require more urgent and immediate efforts.

Consequently, many countries have become more HIV endemic, and there has commensurately been a growing expectation from the global community regarding a country's own inability to sustain and even to expand its own response to meet and manage the trajectory of the growing need for prevention and intervention services for its population. Following the Doha Declaration, the WHO Global Price Reporting Mechanism showed that the prices of most first-line regimens for antiretroviral medicines have decreased by 40% to 60% between the years 2006 and 2010.[377] Despite the fact that costs of ARVs are considerably reduced with the use of generic antiretroviral drugs,[378] this reduction does not always extend to LMICs, who, despite the flexibilities that were introduced, such as compulsory licensing, continue to lack manufacturing capacities to reap the full benefit of the flexibilities. [379]

The Doha Declaration also acknowledges each member's right to define a national emergency or a circumstance of extreme emergency in health-related issues.[380] Nevertheless, governments still face challenges from pharmaceutical manufacturers on whether they can issue compulsory licenses over certain medications. Hence, the compulsory licences on medications for chronic diseases such as HIV/AIDS, tuberculosis, malaria and other epidemics are still being interpreted as a restriction on

375 Amir Attaran and Lee Gillespie White, 'Do Patents for Antiretroviral Drugs Constrain Access to Aids Treatment in Africa?' (2002) 286(15) Journal of the American Medical Association, 1886-1892.

376 Joel Pauls Wohlgemut, 'AIDS Africa and indifference: a Confession' (2001) 286(15) Journal of the American Medical Association 1886-1892.

377 Kubo K and Yamane H, Determinants of antiretroviral prices: An analysis of global price reporting mechanism data and https://www.theglobalfund.org/media/10103/corporate_2020resultsreport_report_en.pdf accessed 30 August 2022.

378 F Nakagawa, *et.al*, 'Projected Lifetime Healthcare Costs Associated with HIV Infection' (2015) 10(4) PLoS ONE. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0125018 accessed 02 April 2019.

379 D Nicol and O Owoeye, 'Using TRIPS Flexibilities to Facilitate Access to Medicines' (Bulletin of the World Health Organization 2013) http://dx.doi.org/10.2471/BLT.12.115865 accessed 01 September 2019.

380 Patents and Pharmaceutical Drugs The Need for Change Intellectual Property Law The tension between two goals – encouraging medical research while keeping medical treatments affordable – is as yet unresolved. https://web.stanford.edu/group/journal/cgi-bin/wordpress/wp-content/uploads/2012/09/Siddiqi_SocSci_2005.pdf accessed 30 July 2019.

the right to patents.[381] The administrative burden associated with the procedural arrangements required by the Declaration for notifying the WTO of the mechanism to provide drugs and medicines to countries not having local manufacturing capacity under the WTO's 2003 Decision is also cumbersome, costly and time consuming for LMICs, especially during an outbreak of disease.[382]

The next section will briefly consider the benefit and role of the UNITAID-supported Medicines Patent Pool and the introduction of free trade agreements in alleviating the situation in LMICs regarding access to ARVs in view of their unique constraints.

3.5 Role of the Medicines Patent Pool and Free Trade Agreements

The objective of the Medicines Patent Pool is to facilitate access to patents to enable competitive generic medicines production and the development of improved products.[383] In 2010, UNITAID, a global health agency hosted by the WHO, has, through Medicines Patent Pool (MPP), negotiated licenses which are either voluntary or compulsory in support of the manufacture of HIV medicines.[384] The MPP developed a patent database for selected HIV medicines. However, the database has some limitations:[385]

- in some cases, the data is outdated;
- the database focusses on a selected number of patents per ARV;
- the database may not be a comprehensive list; and
- there may be other relevant patents that are not yet identified.[386]

Member States are hence advised to consult with their national or regional offices for the most up to date information on the current database. Moreover, the issuance of voluntary licences and MPP have distorted access by encouraging a new type of

---

381 Under compulsory licencing the generic copy of the medicine is produces mainly for the domestic market and not for export. WTO, Compulsory Licensing of pharmaceuticals and TRIPS updated March 2018.

382 Item 1 of the 'Decision On Template For The Notification Of Preferential Rules Of Origin For Least Developed Countries' (Adopted on 2 March 2017).

383 Ellen Hoen, *et al*, 'Driving a decade of change: HIV/AIDS, patents and access to medicines for all' (NCBI 27 March 2011) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3078828/ accessed 01 September 2019.

384 'UnitAID Medicines Patent Pool' (UnitAID 13 July 2015) https://unitaid.org/news-blog/unitaid-medicines-patent-pool-publish-hiv-drug-patent-survey/#en accessed 31 July 2019).

385 https://medicinespatentpool.org/what-we-do/medspal/ accessed 16 September 2019.

386 'UnitAID Medicines Patent Pool' (UnitAID 13 July 2015) https://unitaid.org/news-blog/unitaid-medicines-patent-pool-publish-hiv-drug-patent-survey/#en accessed 31 July 2019.

monopoly in LMICs as “funders are leaving many middle-income countries that will have to pay and provide quality-assured” ARTs out of own limited resources.[387]

Bilateral and regional trade agreement negotiations ushered in a new type of trade negotiations, namely free trade agreements (FTA).[388] A free trade agreement (FTA) is a form of consent between two or more countries where the countries agree on certain obligations that affect trade in goods and services, and protections for investors and intellectual property rights, among other topics. [389] South Africa, among others, is part of several free trade agreements, such as the one with Botswana, Lesotho, Namibia, and eSwatini, which comprises the Southern African Customs Union (SACU); the Southern African Development Community (SADC) Free Trade Agreement; and the European Union-South African Trade and Development Cooperation Agreement. South Africa is also a member of the newly launched African Continental Free Trade Area (AfCFTA).

The FTAs transcend the requirements of the TRIPS Agreement (termed TRIPS-plus rules). All of the FTAs incorporate and introduce IP rules that are more stringent than the global IP standards of TRIPS agreement, where the IP clauses in the existing FTAs are now a benchmark for the affected countries.[390] The following clauses in existing FTA negotiations may negatively impact on South Africa’s manufacturing of generic drugs through the limitations of the TRIPS’ flexibilities, for example:[391]

- Patent extension term for unnecessary delays by introducing “adjustments” of between three to five years for these delays. These extend patent life beyond TRIPS’ 20-year period;
- Compulsory licensing restrictions: limitations on the export of drugs under compulsory license were proposed by the US in the current Free Trade Agreement of the Americas (FTAA) negotiations. This undermines the mechanism of the WTO General Council Decision of 30th August 2003, discussed above. The restrictions are contrary to the spirit of the Doha Declaration which allows Members the freedom to decide their own regime;

---

387 EJ Beck*, et al,* ‘Does the Political Will Exist to Bring Quality-Assured and Affordable Drugs to Low- and Middle-Income Countries?’ (2019) 12(1) Glob Health Action.

388 FTA between Thailand and the USA & EU, FTA between India and the EU, Trans-Pacific Partnership Agreements (TPPA), AND Regional Comprehensive Economic Partnerships (RCEP), between ASEAN and six countries (Japan, South Korea, India, Australia, New Zealand and China).

389 International Trade Administration. Free Trade Agreement Overview. https://www.trade.gov/free-trade-agreement-overview accessed 6 October 2021.

390 P Roffe and D Vivas-Eugui, ‘A Shift in Intellectual Property Policy in US FTAs?' (August 2007) http://www.iprsonline.org/ictsd/news/bridges11-5.pg15-16.pdf accessed 31 July 2019.

391 https://www.genome.gov accessed 22 October 2018.

- Exclusive rights over test data: owners of patented drugs that have not yet been marketed or registered in a country are granted exclusivity over test data on safety and efficacy for a period of five years, as is the case in the US-Chile FTA Central America Free Trade Agreement (CAFTA). This protection also extends to off-patent drugs, meaning that patients need to wait five extra years before generic drug manufacturers can use the data to make generic versions of the drug. There are no provisions for such rights in the TRIPS Agreement; and
- Marketing authorisation: CAFTA grants drug regulatory authorities' new responsibilities in assessing the patent status of a drug before granting marketing authorisation for a generic drug. This could be harmful, as these regulatory authorities do not have the experience to make decisions on patents. Moreover, CAFTA requires that generic manufacturers get the consent of patent owners to use the safety and efficacy data in order to obtain marketing authorisation. Since generic manufacturers cannot afford to re-do these tests, this could effectively undermine compulsory licensing permitted by TRIPS.[392]

Concern regarding priority rights reflected in the FTAs, such as those referred to above, does not only appear through the international multilateral lens and arrangements, but also through regional and bilateral agreements.[393] The potential impact of FTAs is that they may negatively affect the South African manufacturing context for generic HIV drugs, extending also to the entire Sub-Saharan region.[394] South Africa accepted the protocol amending the TRIPS Agreement and deposited its instrument of acceptance for the 2005 TRIPS protocol on 23 February 2016. Access to ARVs, however, remains a cause for concern, as some of the following major originator companies holding ARV patents, e.g., Abbott, Boeringer Ingelheim (BI), Bristol–Meyers Squibb (BMS), Gilead, GlaxoSmithKline (GSK), Merck, Pfizer, Roche, and Tibotec,[395] also acquired patent rights in some of the African states, including South Africa.[396]

A case in point relates to the recent example that occurred in South Africa in 2015, when a drastic shortage of Lopinavir/Ritonavir (LPV/r) compromised PLWH's access

392 https://www.trade.gov/cafta/ accessed 31 July 2019.

393 Patents allow patent-holders to extend, or 'evergreen' their monopolies. Pogge Revista 'De Economía Institucional' (2008) 10(19), Second Semester. Also see https://www.genome.gov accessed 22 October 2018.

394 K Satyanarayana and S Srivastava 'Poverty, health & intellectual property rights with special reference to India' (2007) 126(4) Indian Journal of Medicine 390-406.

395 K Satyanarayana and S Srivastava 'Patent pooling for promoting access to Antiretroviral drugs (ARVs) a strategic option for India' (2010) 4 Open AIDS Journal 41–53.

396 Carlos Correa, 'Flexibilities provided by the Agreement on Trade-Related Aspects of Intellectual Property Rights' (2018) 96(3) Bull World Health Organization 185–193.

to ARVs. AbbVie, a holder of a key HIV medicine patent, prevented the use of generic versions of LPV/r in South Africa, as well as refused providing voluntary licences to the Medicines Patent Pool, which would improve security of LPV/r supply in LMICs.[397] In December 2015, it was announced by the Medicines Patent Pool (MPP) that after negotiations with the South African National Department of Health, a new licensing agreement was signed with AbbVie in order to address future demands for HIV treatment Lopinavir/Ritonavir (LPV/r) in South Africa and across Africa. Under the agreement, generic ARV manufacturers, upon obtaining a sublicense from MPP, will be permitted to manufacture and sell generic versions of LPV/r throughout Africa, as well as combinations of Ritonavir with other ARVs.[398]

3.6 Paris Convention for the protection of intellectual property and "priority rights"

The Paris Convention, adopted in 1883, applies to industrial property in the widest sense, including trademarks, patents, utility models, industrial designs, service marks, geographical indications, trade names, as well as the repression of unfair competition.[399] This international agreement was the first initiative aimed at assisting creators to ensure protection of their intellectual works in other jurisdictions. The Paris Convention encourages the filing of patent registrations in priority countries as a subsequent move to "priority rights". Article 4B of the Convention explains this as follows:[400]

> "[A]n Applicant who filed an intellectual property right application (Patent, Utility Model, Industrial Design, Trademark) in a first country can preserve for the purpose of legal validity the time rank of that application for a subsequent filing in a second country. Another way of viewing a priority right may be to see it as an option to preserve the time rank of the application in a first country for a subsequent application in a second country if that option is exercised within a certain priority time period and if certain requirements are fulfilled."[401]

Regrettably, South Africa has fallen prey to the notion of priority rights, as it has authorised more than thirteen pharmaceutical patents for HIV drugs without any thorough check on the status of the existing patent at the country of origin and the

---

397 Press Release 27 October 2015 South Africa should override patent on key HIV medicine after widespread stock out problem. https://www.msf.org/south-africa-should-override-patent-key-hiv-medicine-after-widespread-stock accessed 07 July 2019.

398 UNITAID 'The Medicines Patent Pool and AbbVie sign licensing agreement to increase access to crucial HIV treatments throughout Africa. 10 December 2015' https://unitaid.org/news-blog/medicines-patent-pool-abbvie-sign-licensing-agreement-increase-access-crucial-hiv-treatments-throughout-africa/#en accessed 6 October 2021.

399 WIPO 'Paris Convention' https://www.wipo.int/treaties/en/ip/paris/ accessed 6 October 2021.

400 'Article 4B of the Paris Convention' https://www.wipo.int/treaties/en/ip/paris/ accessed 6 October 2021.

401 http://www.wipo.int/wipolex/en/treaties/text.jsp?file_id=288514#P83_6610 accessed 24 June 2019.

implication of such issuance of the patent on drug costs.[402] A serious indictment against South Africa as far as patents are concerned, is that South Africa is not an examining country, which means that the content of patent applications is not examined[403] to determine whether they meet the requirements for patentability and a possible extension of the patent.[404] Multinational pharmaceutical companies are originator companies for HIV drugs, thus their huge presence rely heavily on the notion of 'ever-greening' that appears to be promoted by the South African Patent Act.[405]

3.7 The South African riposte to the Doha Declaration and the accentuation to access health care

The global recognition of accessing health care and health care services as a right by the WHO in 1946, particularly championed by the UN, is one of the most significant developments of the past century.[406] As stated earlier in this chapter, section 27 of the South African Constitution,[407] read together with section 1 of the National Health Act 61 of 2003,[408] acknowledges and stipulates that everyone is entitled to "access to health care services, including reproductive health care".[409]

The manufacturing of generic drugs are influential in the Sub-Saharan African public health care system, with South Africa becoming a giant distributor of generic ARVs to the region.[410] While the generic drug supply chain and the brand drug supply-chain include many of the stakeholders, the essential manufacturers of the ARVs remain the multinational pharmaceutical companies that still manufacture, distribute and manage

---

402 Lonias Ndlovu, 'South African Patent Law and Access to Medicine' (Research Gate November 2013) https://www.researchgate.net/publication/264236381_South_African_Patent_Law_and_Access_to_Medicines accessed 30 July 2019.

403 Section 25 (4) of the Patent Act 57 of 1978 read together with Regulation 40 assert that the Registrar of Patents should examine the applications that are set before him/her for consideration. However, based on the number of patents issued, a disparity is noticeable that "in practice the Registrar does not ensure compliance with the Act." See E Zdravkova E, Patent Protection in South Africa (presentation), WTO/WHO/WIPO and Dti Intellectual Property and Public Health Workshop, 7-8 August 2013.

404 RM Anderson, RM May and AR McLean, 'Possible Demographic Consequences of AIDS in Developing Countries' (1988) 332 Nature 228-34.

405 Section 25 of the South African Patent Act, Act 57 of 1978. Efforts to include IP are included in the following amendments: Intellectual Property Laws Amendment Act 38 of 1997 Patents Amendment Act, 10 of 2001 Patents Amendment Act, No. 58 of 2002 GENERAL NOTE In terms of s. 48 of Act 38 of 1997.

406 Article 55 of the UN Charter and Article 25(1) OF THE Universal Declaration of Human Rights.

407 Constitution of the Republic of South Africa, 1996 (hereinafter referred to as "the Constitution").

408 National Health Act 61 of 2003 (Hereinafter referred to as "the Act")

409 The Constitution.

410 Mergen Reddy, 'The Economic And Socio-economic benefits of R&D-based Multinational pharmaceuticals on the South African economy' (Deloitte 2007) http://ipasa.co.za/Downloads/IPASA%20and%20Pharmaceutical%20Industry%20Profile/Research%202007/IMSA%20Book%20071013.pdf accessed 31 July 2019.

centres from South Africa.[411] It is worth mentioning that the multinational pharmaceutical companies will continue to maintain a stronghold on the manufacturing of generic drugs in South Africa.[412]

Public patients in South Africa and in other parts of Africa rely on governments' supply of generic drugs that are less costly.[413] Often debated, and justifiably so, is the notion of access to health care, which has been a pertinent issue for the past few decades in South Africa.

The landmark Constitutional court case of *Soobramoney v Minister of Health*[414] provides the *litmus* test in the determination of the right of accessing health care services in relation to Section 27 of the Constitution. In this case, the ConCourt interpreted the right of access to health care services as being dependent upon the availability of government resources and the obligation to make access to health care services or the realisation of this right "progressively" available. Consequently, scarce resources and the concomitant demand for health care services limits the progressive achievement of this right. Affected by this decision are ARVs in the public context (public hospitals and clinics), whose short supply would constitute a limitation of the gradual realisation of the right to access to health care services, whilst also accentuating the conclusion that access appears to be the privilege of private, and not State patients.

One specific argument holds that access to HIV treatment in South Africa and elsewhere also affects the middle class who have the benefit of access to a medical aid scheme.[415] The high costs associated with medical aid claims, which are the result of the middle- and upper-class acquiring HIV medicines, make them desirable targets for pharmaceutical companies because they can access original drugs for HIV

411 'Compulsory Licensing Request' (CPTech 07 March 2001) http://www.cptech.org/ip/health/sa/ciplanetsh03072001.html accessed 31 July 2019. Competition Commission Newsletter, 'Commission Questions Conduct of Anti-retroviral Companies No. 13' (CompCom 2003) http://www.compcom.co.za/wp-content/uploads/2014/09/Dec-03-Newsletter.pdf accessed 31 July 2019.

412 Yu-Fan Wen and Thapi Matsaneng, 'Patents, Pharmaceuticals and Competition: Benefitting from an effective patent examination system' (CompCom 2014) https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Y+Wen+and+T+Matsaneng+%2C+%E2%80%98Patents%2C+Pharmaceuticals+and+Competition%3A+Benefitting+from+an+effe accessed 31 July 2019.

413 The South African government has taken an offer by GlaxoSmithKline for the manufactory of cheap generic ARVs. Susan Mayor 'GlaxoSmithKline licenses production of generic AIDS drugs in South Africa' (2001) 323(7317) BMJ 828.

414 *Soobramoney v Minister of Health (Kwazulu-Natal)* 1998 (1) SA 765 (CC).

415 Sophie Huddart, *et al*, 'The Doha declaration in action: An examination of patent law flexibilities in the South African acquired immunodeficiency syndrome epidemic' (2017) 5(1) Journal of Health Speciality 30-34.

treatment. In this manner, patent holders are able to tap into both public and private patient pools. [416] Although medical aid membership poses as a privilege and a right of accessing health care, affordability in a perverse sense compromises the right to access affordable health care.[417]

A comparison between private patients (those with access to private medical aid) and public patients (those relying on public resources) shows a clear disparity of access to ARV drugs. Current pharma-economics in South Africa confirm the disparity between private and public access in that the pharmaceutical market in SA was valued at approximately R45 billion in 2015. The private sector accounted for 84% of the market, compared to the public sector accounting for 16% of the market.[418]

Traditionally, accessing health care services has been more available to those who belong to private medical schemes. The notion of patents inadvertently creates disparity between the 'have's' and the 'have not's' in South Africa. The duty to provide and facilitate access to health care for PLWH needs assertion, based on Constitutional imperatives. Access to ARVs has been a recurring factor in South Africa's quest for a recognition of the right to access health care and health care services for decades. The enormity created by costs of the ARVs makes the encounter an even more compelling issue requiring attention, as in a large measure, the global HIV and AIDS crisis impacts on the issue of access to *affordable* medicines in many of the LMICs.[419]

In attempting to address some of the challenges relating to the management of HIV and AIDS and access to ARVs, the United Nations Security Council on AIDS adopted its first-ever resolution on a health issue in 2000.[420] The resolution recognises the efforts of the Member States which have acknowledged the problems and where

---

416 In 1994 a country's health care system was based on a two-tiered approach where approximately 20% of populations, mostly white, was covered by private health care, while the black majority relied on public sector care characterized by "irrational use of resources, poor working conditions and inadequate infrastructure. See South African Department of Health, National Drug Policy for South Africa 3 (1996).

417 Competition Commission of South Africa, 'Statement of information by consumer project on technology concerning an alleged prohibited practice' in Tau and others v. GSK and Boheringer Ingelheim. http://www.section27.org.za/content/uploads/2010/10/TauvGSKevidenceAndLegalSubmissions.pdf accessed 31 July 2019.

418 Directorate: Pharmaceuticals and Medical Devices National Department of Trade and Industry (28 June 2017) https://pmg.org.za/committee-meeting/24697/ accessed 07 December 2022.

419 The TRIPS flexibilities and the introduction of Medicines Patent Pool are working to increase access to lifesaving medicines. https://medicinepatentpool.org accessed 01 September 2019.

420 UN Security Council Resolution 1308 (2000) on the Responsibility of the Security Council in the Maintenance of International Peace and Security: HIV/AIDS and International Peace-keeping Operations 17 July 2000.

applicable, have developed national programmes.[421] The 54th session of the United Nation's Security Council's General Assembly welcomed the decision to include in the agenda, an additional item of an urgent and important character, entitled "Review of the problem of HIV/AIDS in all its aspects".[422] The main objective of these resolutions has been and remains to encourage cooperation with the international community and UNAIDS, and where appropriate, to give effect long-term strategies for HIV and AIDS. The Security Council, monitored by the General Assembly Declaration of Commitment on HIV and AIDS, recognised the epidemic as a "global crisis" that calls for global action.[423]

It would appear that South Africa found safeguard in the resolution when it stood its ground against TRIPS Agreement by the inclusion of section 15C into the Medicines and Related Substances Act, discussed in more detail below. The Security Council encouraged Member States to adopt programmes to educate prevent, encourage voluntary confidential testing and counselling and promote access to treatment of their personnel, and the public in general.[424]

South Africa responded to the new rules prescribed by TRIPS and its FTA cohorts by taking the battle to the streets through demonstrations by civil right groups, as well as through the judicial system.[425] The TAC and other non-governmental organisations (NGOs) took a stance against the IPs, especially to counter the impact of patents on ARVs, as social and political pressures in South Africa mounted on the government to address the HIV epidemic effectively.[426] In January 1996, the then Minister of Health, Dr Nkosazana Dlamini-Zuma, set forth a number of different objectives designed to address health issues relating to HIV, including lowering drug prices, supporting the development of a local pharmaceutical industry for the local production of essential drugs, and promoting the prescription of generic drugs in both the public and private

421 https://admespipp.blogspot.com/2015/12/un-pulse-dag-hammarskjold-library.html accessed 01 September 2019.

422 The Security Council passes resolution 1983 (2011) on the impacts of Hiv/Aids epidemic in conflict and post-conflict. https://digitallibrary.un.org/record/705437?ln=en accessed 01 September 2019.

423 http://www.who.int/bulletin/volumes/94/4/16-172882/en/#R3 accessed 19 September 2018.a

424 http://www.who.int/bulletin/volumes/94/4/16-172882/en/#R3 accessed 19 September 2018.

425 KM Leisinger, LF Garabedian, and AK Wagner, 'Improving access to medicines in low- and middle-income countries: corporate responsibilities in context' (2012) 5(2) Southern Med Review 3–8.

426 Stiglitz J, 'Scrooge and intellectual property rights' (BMJ 21 December 2006) https://doi.org/10.1136/bmj.39048.428380.80 accessed 15 September 2019.

sectors.[427] These efforts were lauded by legal scholars, in particular the former Constitutional Court Judge, Justice Cameron, who stated as follows:

> "[I]t was brave, principled, imaginative campaigning by South Africa's Treatment Action Campaign (TAC). Its moral challenges to drug pricing shook the world awake. TAC refused to accept that lifesaving treatment – treatment that was available and that could be cheaply produced – would not be given to poor people, most of them black, because of laws protecting intellectual property and securing patent-holders' profits."[428]

This observation underscores the fact that the real political and economic consequences of patents on the procurement of ARVs should be informed by the understanding that the governance of ARVs procurement requires a meaningful analysis of the interface between national and international actors. The afore-going discussion highlighted that the chief concern for LMICs was the difficulty of accessing affordable medicines under the TRIPS regime.[429]

Dr Dhlamini-Zuma sought advice from a Pricing Committee, which was established in respect of Section 22G of MRSA.[430] The court's decision on section 15C of the MRSA, which offers hope to PLWH, spawned heated debates in South Africa and the USA, as will be discussed in more detail below. The workable compromise brought about by section 15C encouraged FTA negotiations beyond the requirements of TRIPS Agreement (termed TRIPS-plus rules).[431]

As described above, LMICs gained a few concessions in the post-TRIPS era in the form of Doha Declaration,[432] which would have provided them the opportunity to invoke the emergency stipulations of the Agreement in times of need to access essential medicines for their respective citizens.

---

427 'South African Department of Health, National Drug Policy for South Africa' (1996) https://www.gov.za/documents/national-drugs-policy accessed 16 September 2019.

428 Edwin Cameron, 'The fundamental barriers to access to medicine remain when they don't need to' (Daily Maverick 24 October 2018) https://www.dailymaverick.co.za/article/2018-10-24-the-fundamental-barriers-to-access-to-medicine-remain-when-they-dont-need-to/ accessed 16 September 2019.

429 Lisa Ann Richey and Stine Jessen Haakonsson, 'Access to ATV Treatment: Aid, Trade and Governance in Uganda' (2014) https://www.files.ethz.ch/isn/18786/Access_ARV_Treatment.pdf accessed 02 August 2019.

430 Andy Gray Fatima Suleman Bada Pharasi, 'South Africa's National Drug Policy : 20 years and still going?' (South African Health Review 01 December 2017) https://hdl.handle.net/10520/EJC-c80c69129 accessed 14 October 2021.

431 Jamie Eisenfeld and François Serres African Legal Developments in the United States and Sub-Saharan Africa' (FALL 2001) 35(3) The International Lawyer.

432 Stine Jessen Haakonsson and Lisa Ann Richey, 'Trips and Public Health: The Doha Declaration and Africa', (2007) 25(1) Development Policy Review 75–90.

The deliberations of the Uruguay Round of Negotiations created great anxiety on the part of the South African government.[433] The then Minister of Health held the view that the public sector prescription drug shortages and the exorbitant prices in the private sector were caused by pricing strategies introduced by patent-holding multinational pharmaceutical conglomerates in South Africa on most ARVs.[434] The South African Pharmaceutical Manufacturers Association (PMA) objected to this view, claiming that their South African government rates were less than those provided to global aid organisations, and that any public sector shortages were the result of rampant pharmaceutical theft.[435] Furthermore, the PMA argued that dropping drug prices would not resolve the access problem due to South Africa not having adequate sufficient for the distribution of drugs.[436]

The PMA lodged a complaint with the Public Protector of South Africa, stating that Department of Health officials made offending media statements that created "a perception in the minds of the general public that medicines in South Africa are unreasonably expensive" and that "the blame for such expensive medicines lies with the manufacturing and primary importing companies."[437] The South African government's concern initially focused more on affordability and not so much on "distribution", as the then Minister of Health's subsequent proposed change to Section 15 (through the insertion of Section 15C)[438] of the Medicines and Related Substances Control Act was believed to address the unreasonably high ARV prices compared to those abroad.[439] Section 15C of the MRSA now reads as follows:

> "The Minister may prescribe conditions for the supply of more affordable medicines in certain circumstances so as to protect the health of the public, and in particular may -

---

433 PieterJ. Kuijper-observed that "The conclusion and the implementation of the Uruguay Round by the European Community proved to be an arduous and long drawn-out operation. In particular the conclusion of the WTO Agreement and its Annexes, caused fundamental legal problems related to the division of powers between the Community and the Member States".

434 Amir Attaran & Lee Gillespie-White, 'Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?' (20001) 286(15) Journal of the American Medical Association 1886-1888.

435 'All Things Considered' (12 January 1998), http://www.npr.org/templates/story/story.php?storyId=1036870 accessed 30 September 2021.

436 Sabin Russell, 'New Crusade to Lower AIDS Drug Costs' (The San Francisco Chronicle 24 May 1999) https://www.sfgate.com/health/article/New-Crusade-To-Lower-AIDS-Drug-Costs-Africa-s-2929307.php accessed 30 September 2019.

437 Public Protector of the Republic of South Africa, Report on the Propriety of the Conduct of Members of the Ministry and Department of Health Relating to Statements in Connection with the Prices of Medicines and Utilisation of Generic Medicines in South Africa, Special Report No. 6 (1997).

438 Long title substituted by Section 37 of Act 65 of 1974, Section 15 of Act 17 of 1979, and Section 22 of Act 94 of 1991.

439 G Donald and JT McNeil, 'South Africa's Bitter Pill for World's Drug Makers' (The New York Times March 29, 1998) https://www.nytimes.com/1998/03/29/business/south-africa-s-bitter-pill-for-world-s-drug-makers.html accessed 30 September 2019.

(a) notwithstanding anything to the contrary contained in the Patents Act, 1978 (Act 57 of 1978), determine that the rights with regard to any medicine under a patent granted in the Republic shall not extend to acts in respect of such medicine which has been put onto the market by the owner of the medicine, or with his or her consent;

(b) prescribe the conditions on which any medicine which is identical in composition, meets the same quality standard and is intended to have the same proprietary name as that of another medicine already registered in the Republic, but which is imported by a person other than the person who is the holder of the registration certificate of the medicine already registered and which originates from any site of manufacture of the original manufacturer as approved by the council in the prescribed manner, may be imported;

(c) prescribe the registration procedure for, as well as the use of, the medicine referred to in paragraph (b)."

The PMA was concerned that the South African government's stance and the proposed legislative change would attract more support from activists that vied for lower drug prices. The debatable legislative proposal encompassed the direct authorisation of parallel imports of patented pharmaceuticals. Dr Ian Roberts, a consultant to Dr Dhlamini-Zuma,[440] drafted the proposal and largely used the language of a draft WIPO patent treaty.[441]

The proposal passed the parliamentary subcommittee for Health and was strongly supported by then President Nelson Mandela.[442] The primary purpose with the insertion of Section 15C into the MRSA was for enabling South Africa's benefit from reduced prices overseas for similar drugs. Despite strong opposition from the international pharmaceutical industry, President Nelson Mandela signed the legislative amendment to the MRSA into law on December 12, 1997.[443]

In an effort to restrain the application of the amendments, the pharmaceutical conglomerates took the matter to Court and contested the constitutionality of the amended MRSA before the High Court of South Africa in February 1998. With respect to Section 15C, the plaintiffs argued:

"that it entailed an impermissible delegation of powers from the legislative to the executive branch of government, because the Minister of Health was authorised to determine the application of patent rights irrespective of the South African Patents

440 W William, II Fisher and CP Rigamonti ,'The South Africa AIDS Controversy A case Study in Patent Law and Policy' (Harvard Law School, 10 February 2005) https://cyber.harvard.edu/people/tfisher/South%20Africa.pdf accessed 07 December 2022.

441 M Frederick, 'WTO TRIPS Agreement and its Implications for Access to Medicines in Developing Countries' (SSRN 09 September 2011) https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1924420 accessed 25 September 2019.

442 https://pharmaphorum.com/sales-marketing/are-dual-arvs-the-new-frontier-in-a-maturin accessed 18 October 2018.

443 W William, II Fisher and CP Rigamonti ,'The South Africa AIDS Controversy A case Study in Patent Law and Policy' (Harvard Law School, 10 February 2005) https://cyber.harvard.edu/people/tfisher/South%20Africa.pdf accessed 07 December 2022.

> Act, and because she was authorised to determine the conditions for the supply of more affordable medicines without any limiting guidelines, that it would enable the Minister of Health to deprive intellectual property owners of their property without compensation in violation of Article 25 of the South African Constitution, and that it was a violation of Article 27 of TRIPS and, because TRIPS binds South Africa, also a violation of sections 44(4) and 231(2)-(3) of the South African Constitution."[444]

The South African government defended the insertion of Section 15C on two grounds, namely that:

1. Section 15C was Constitutional, because the Minister of Health was not granted overarching powers for abrogating patent rights; and
2. It was maintained that Section 15C adhered to TRIPS, contending that TRIPS would not prevent parallel imports, and that Section 15C did not cover the compulsory licensing controversy.[445]

Fearing exposure of exorbitant pricing of HIV drugs in the developing world, the US government-backed pharmaceutical industry vigorously refuted and contested the enactment of Section 15C, arguing that "it was tantamount to a complete abrogation of patent rights and that it violated the Agreement on TRIPS".[446] On 6 May 2001, the case was adjourned, following threats from the PMA to file an appeal on the grounds that they needed additional time to respond, among others, to issues raised by Treatment Access Campaign (TAC), who had been granted *amicus curiae* status.

On 16 October 2003, the South African Competition Commission found that the pharmaceutical (firms GlaxoSmithKline South Africa (Pty) Ltd (GSK) and Boehringer Ingelheim (BI)) contravened the Competition Act No. 89 of 1998. These conglomerates were found to be abusing their leading roles in their respective ARV markets on the ground of excessive pricing, among others.[447]

The legal salience of this precedent-setting decision, which signals the first good faith implementation of the Doha Declaration on the TRIPS Agreement and Public Health, which prioritises the health of the public over monopolistic patent protection. In the words of one commentator, the decision validates three important competition theories, namely:

---

444 The Constitution.

445 World Health Organization, World Trade Organization and World Trade Organization Agreements and Public Health 106 (2002).

446 Note that American subsidiaries accounted for 27% of the pharmaceutical market in South Africa, which was more than South African firms had; see Lynne Duke, Nkosazana Zuma – Activist Health Minister Draws Foes in S. Africa, Washington Post (December 11, 1998).

447 http://www.cptech.org/ip/health/sa/cc10162003.html accessed 04 September 2021.

> "It clarifies: (a) that drug companies' monopoly prices, even when partially discounted, can unnecessarily impede access to medicines; (b) that the refusal of drug companies to issue voluntary licenses to generic competitors can abusively impede competition; and (c) that the refusal to grant licenses can prevent manufacture of fixed-dose combination medicines, thereby complicating patient adherence to multi-pill treatment regimes."[448]

Moreover, the TRIPS Agreement and Public Health also allows the granting of an obligatory licence that would permit the production of ARVs within South Africa, as well as the export of these ARVs to other developing countries.

3.8 Access to ARVs in the aftermath of Doha and the PMA debacle

Despite the South African government's efforts described in this chapter, aimed at addressing the unaffordability of ARVs, it found itself again in the spotlight when its policy with regard to its 2001 programme addressing the prevention of mother-to-child-transmission of HIV was challenged, which restricted the availability of Nevirapine to limited sites in each province, serving only served about 10% of the population. The result of this policy was that pregnant mothers without access to the State's satellite clinics and private health care, did not have access to ARVs. This situation led to the TAC challenging the government to reasons as to why Nevirapine could not be made available to patients in the public health sector, leading to an action against the SA government, based on the provisions that the government had, *inter alia*, violated the rights of women to access health care services.[449]

The High Court ruled that there was a degree of unreasonability by the government in refusing Nevirapine availability in the public health sector and ordered government to issue ARVs in public hospitals where medically indicated.[450] The government then appealed this decision to the Constitutional Court. Whilst the TAC's argument was based on the State's obligation to issue health care services to prevent MTCT, the government's responses were, among others, that the efficacy of Nevirapine was questionable and national capacity was inadequate to serve all pregnant women in the public sector. The Constitutional Court held that the government's measures to achieve the gradual realisation of the right to access health care services, and consequently ordered the government to provide ARVs to pregnant women infected with HIV/AIDS in order to prevent MTCT.[451]

---

448 South African Competition Commission announces stunning victory for access to cheaper drugs, holds GlaxoSmithKline and Boehringer Ingelheim responsible for excessive pricing and other anti-competitive practices. See http://www.cptech.org/ip/health/sa/hgap10172003.html accessed 04 September 2021.

449 *Treatment Action Campaign v Minister of Health* 2002(4) BCLR 356 (T).

450 *Treatment Action Campaign v Minister of Health* 2002(4) BCLR 356 (T).

451 *Minister of Health v Treatment Action Campaign* 2002 (5) SA 721 (CC)

It is clear from this judgment that South Africa's journey to promote access to affordable ARVs to its citizens has been a long and painful one.

3.9 National Advisory Group on HIV/AIDS (NACOSA)

During the 1990s, South Africa developed a national drug policy in collaboration with the World Health Organisation and the appointment of a body, the National Advisory Group (NACOSA) on HIV/AIDS, tasked to develop more comprehensive government policies for HIV/AIDS.[452] Currently, the National Advisory Group consists of a network of over 2,500 civil society organisations working together to promote efforts addressing HIV, AIDS and TB in Southern Africa through dialogue, capacity building and technical assistance, focusing particularly on women, young girls and children.[453] As a principal recipient of the Global Fund and in partnership with USAID and PEPFAR and other public and private sector partners, NACOSA works at all levels—from international agencies and national government, right though to sub-district services and small, community groups.

Furthermore, the NACOSA developed a policy to secure the right to universal access to essential medicines by committing the government to:

- ensure the accessibility and availability of critical medicines to all citizens;
- ensure the efficacy, safety and quality of drugs;
- ensure good dispensing and prescription practices;
- advance the reasonable use of drugs by dispensers, prescribers and patients by providing the requisite education, training and information; and
- advance the concept of individual accountability for health, preventive care and informed decision-making.[454]

3.10 Intellectual property policy

Subsequent to the implementation of Section 15C,[455] the South African government gradually began realising the gaps that exist in the IP laws and policies. These gaps propelled the government to revamp the existing legislation on patents. A

---

452 https://www.sahistory.org.za/topic/history-official-government-hivaids-policy-south-africa (accessed 01 September 2019).

453 NACOSA. https://www.nacosa.org.za (accessed 07 October 2021).

457 Government Gazette No. 41870 31 AUGUST 2018.

455 Medicines and Related Substances Act NO. 101 of 1965, 15C inserted by s. 10 of Act No. 90 of 1997.

comprehensive policy on IP was published in Government Gazette 41870, discussed in more detail below.[456]

Since the South African strategy (expressed in the National Development Plan (NPA) 2030) seeks to employ a comprehensive IP policy, definite goals should set on health-related issues, which have to be aligned to the existing national laws as well as international standards.[457]

Justification for the manufacturing of ARVs in South Africa has to integrate a balance of the need for patenting,[458] as well as other considerations espoused in the IP Policy. Current legislation, (e.g., the Intellectual Property Rights from Publicly Financed Research and Development Act (the Act))[459] is limited to publicly financed innovation and addresses only the concerns in publicly financed research and development. Accessing health care services is not confined to the currently applicable machinery of the Act. Therefore, a policy is required to facilitate innovation, research and development across both the public as well as the private spheres.

As an important policy instrument, appropriate IP policy will assist in curbing the high pricing of medicines. Therefore, South Africa needs to shift towards a knowledge economy, where industry is involved in the local manufacturing of medicines under the auspices of a conducive IP policy; which is one of the core legal frameworks necessary to enable South Africa to spearhead the patenting regime in order to benefit the South African development in health care.

3.10.1 The objectives of the intellectual property policy

The South African IP policy seeks to advance the following objectives:[460]

- engendering the Constitution's ethos;
- aligning the IP structure to the country's NDP and overall industrial policy;
- developing an integrated inter-Ministerial perspective to IP;
- striking an equilibrium between the IP users and owners;
- stimulating genuine creativity;
- facilitating key industrial development and balancing with the public's interest;

---

456 Government Gazette No. 41870 31 AUGUST 2018.

457 http://www.section27.org.za/wp-content/uploads/2013/01/ndp2030_chap10.pdf accessed 20 January 2022

458 https://www.msf.org.za/news-and-resources/press-release/south-africa-stop-blindly-handing-out-patents accessed 20/ accessed 05 January 2022

459 Intellectual Property Rights from Publicly Financed Research and Development Act 51 of 2008.

460 Intellectual Property Policy Of The Republic Of South Africa Phase In the Department Of Trade And Industry Notice 518 Of 2018 Government Gazette, No. 41870 Of 31 August 2018

- fostering technology and investment diffusion;
- adopting an integrated IP strategy in sub-regional, regional and international forums;
- promoting public health; and
- adhering to global obligations, particularly those on human rights.

South Africa has the legislative acumen to apply IP to advance the health care, accessing health care services, as well as promoting the national economy. This legal framework includes, among others, the Intellectual Property Rights from Publicly Financed Research and Development Act,[461] National Environmental Management: Biodiversity Act,[462] Patents Act,[463] Merchandise Marks Act,[464] Copyright Act,[465] Designs Act,[466] Plant Breeders' Rights Act,[467] and the Trademarks Act.[468]

Together with the above-listed of objectives of the IP Policy, these statutes establish the constitutionality of IP Policy because they are strong enough in supporting the government's intentions to participate in the development of a people-focused health care system.

3.10.2 Intellectual property and public health

Regarding access to medical health care, the NDP's Visio 2030 encourages that "[a] health system that works for everyone and produces positive health outcomes is not out of reach. It is possible".[469]

In pursuit of the Constitutional entrenchment of section 27, South Africa needs a broader participation by all the national pharmaceutical companies in terms of which the National Industrial Policy Framework (NIPF),[470] implemented through the Industrial Policy Action Plan (IPAP)[471] will be invoked. Furthermore, PGx requires political buy-in for its functionality. An agreement at political level that recognises that IP is an important endeavour towards national development is still not a settled issue. A report

461 Intellectual Property Rights from Publicly Financed Research and Development Act 51 of 2008.
462 Biodiversity Act 10 of 2004.
463 Patents Act 57 of 1978.
464 Merchandise Marks Act 17 of 1941.
465 Copyright Act 98 of 1978.
466 Designs Act 195 of 1993.
467 Plant Breeders' Rights Act 15 of 1976.
468 Trademarks Act 194 of 1993.
469 http://www.section27.org.za/wp-content/uploads/2013/01/ndp2030_chap10.pdf accessed 19 January 2022.
470 https://www.gov.za/sites/default/files/gcis_document/201409/national-industrial-framework-policy04032008.pdf accessed 2 January 2022
471 http://www.thedtic.gov.za/wp-content/uploads/Industrial_Policy_Action_Plan2015.pdf accessed 20 January 2022

from the WIPO Secretariat regarding South Africa's patent system concluded that "[i]nconclusive empirical evidence on the role of the patent system to encourage research and development (R&D) and technology transfer makes it difficult to draw any clear-cut conclusion about the effectiveness of the patent system for economic development". Tomlinson *et al.* present nine case studies to illustrate how systemic shortcomings in South Africa's patent laws have negatively impacted on the access of medicines for treating a diversity of diseases in both the public and private sectors.[472] These case studies explain how the flawed system has permitted pharmaceutical companies to prolong their monopoly periods in South Africa for many years and even decades after the expiry of their patent protections in other parts of the world, to the detriment of millions of patients in South Africa.[473]

3.10.3 Intellectual property policy (phase 1)[474]

In May 2018, Cabinet approved Phase 1 of the IP Policy which offers concrete suggestions on the tailoring of IP through the Department of Trade and Industry (DTI) office. The policy is said to affect medicines produced locally and introducing product development partnerships that will advantage the local ARVs market and improve on affordability of HIV drugs.[475]

A major problem identified in advancing the role of IP in public health is that South Africa does not conduct a substantive search and examination (SSE) prior to the granting of patents. South African patent laws require that the Registrar of Patents, housed within the Companies and Intellectual Property Commission (CIPC), only conducts examination in relation to the formalities of the application. This approach is referred to as a "depository system" in terms of which the subject of a patent application is only examined against the substantive criteria of novelty, inventive step, and industrial applicability if the patent is challenged in litigation, such as in relation to infringement or revocation.[476]

---

472 Catherine Tomlinson, *et* al,'Patent Barriers to Medicine Access in South Africa: A Case For Patent Law Reform' (Papers 27 September 2016) https://infojustice.org/archives/36977 accessed 07 December 2022.

473 Catherine Tomlinson, *et* al,'Patent Barriers to Medicine Access in South Africa: A Case For Patent Law Reform' (Papers 27 September 2016) https://infojustice.org/archives/36977 accessed 07 December 2022.

474 Intellectual Property Policy (2018; Phase 1)'. .https://www.gov.za/sites/default/files/gcis_document/201808/ippolicy2018-phasei.pdf accessed 07 October 2021.

475 The South African Intellectual Policy. https://spoor.com/south-africa-ip-policy/ accessed 30 August 2022.

476 The South African Intellectual Policy. https://www.gov.za/sites/default/files/gcis_document/201808/41870gen518_1.pdf (accessed 16 November 2022).

The IP Policy proposes major reforms that will also promote and advance South Africa's socio-economic development objectives as outlined in national government's key policy documents, such as the National Development Plan (NDP), the New Growth Path Framework (NGP), National Drug Plan, NIPF and the various iterations of IPAP. Some of the reforms of the policy include the following:[477]

- introducing comprehensive patent search and examination (SSE);
- leveraging flexibilities contained in the TRIPS to ensure that South Africa protects IPRs while simultaneously promoting public health, innovation, research and development, food security, environmental considerations, transfer of technology, local manufacture, and broad socio-economic development;
- promotion of regional cooperation and integration in IP;
- commitment to all relevant international obligations South Africa is party to;
- promotion of economic empowerment through, among other means, the implementation of the "utility model" to support the registration of patents by resident small, medium and micro-enterprises (SMMEs), historically disadvantaged individuals, and companies who are operating in the informal sector;
- coordinated approach to creating awareness about IP among South Africans, so as to protect nationally-owned IP that is related to indigenous resources, traditional innovation and traditional knowledge;
- creation of a system for protection for traditional knowledge which will guard against misappropriation and exploitation, as well as promote further research and development into products and services based on traditional knowledge; and
- promotion of international best-practices in IP that align with South Africa's development objectives.

These reforms are to be lauded, yet there is the lingering question of why South Africa has never joined the African Regional Intellectual Property Organisation (ARIPO), or the *Organisation Africaine de la Propriété Intellectuelle* (OAPI), considering that one of the above-cited reforms is geared towards promoting regional cooperation and integration of IP. Despite this, the IP Policy is a progressive effort, particularly since it

[477] Department of Trade Industries, 'Intellectual Property Policy of the Republic of South Africa-Phase I' https://www.gov.za/sites/default/files/gcis_document/201808/41870gen518_1.pdf accessed 07 December 2022.

"is in line with international practices and strikes a fair balance between incentives for innovation and the need to promote generic competition and access to medicine".[478]

3.10.4 Department of Trade and Industry: industrial policy for pharmaceutical industry

For Brooks and Baker,[479] "the unconscionable gap in the affordability of life-saving and life-enhancing HIV medicines, reflect a massive disconnect between the perceived interests of rich countries in the global North and the proprietary pharmaceutical companies that do research, develop, and produce patented medicines, and, on the other hand, the interests of developing countries in the global South."[480] These authors remark that a disconnect occurs at the intersection of two separate systems: national and global intellectual property structures, and global patterns of poverty and income inequality.

Although the full terms and conditions of patent licensing agreements are confidential, patent holders may announce a commitment not to enforce its patents in certain countries through a non-assert declaration that provides a commitment to non-enforcement of patents or provides an immunity-from-suit agreement or similar mechanism.[481] In addition, some of these licensing terms and conditions may:

- specify the countries in which a medicine may be made or sold;
- determine whether fixed dose combinations can be developed;
- provide whether royalties are payable to the patent holder;
- determine which quality criteria need to be met by the licensee; and
- provide a wide range of other provisions that indicate what the licensee may or may not do.[482]

It is submitted that collaboration and innovation, rather than property expropriation, will drive down the price of live-saving drugs. In this context, it is instructive that some key

---

478 UNCTAD, 'South Africa Adopts New IP Policy Improving Access to Medicine' (31 May 2018) https://unctad.org/news/south-africa-adopts-new-ip-policy-improving-access-medicine accessed 18 November 2022.

479 K Brook and JD Baker, 'Patents, Pricing, and Access to Essential Medicines in Developing Countries' (2009) 11(7) Virtual Mentor 527-532.

480 Brooks and Baker(2009) 11(7) Virtual Mentor 527-532.

481 Park C Agrees, 'Limiting the Number of Licensees may Hinder the Robust Generic Competition that can Bring Prices Down' (AIDS Map 26 July 2012) http://www.aidsmap.com/news/jul-2012/intellectual-property-still-threat-antiretroviral-access-says-panel accessed 01 September 2019.

482 National Department of Trade and Industry, 'Intellectual Property Policy' (2018; Phase 1) https://www.gov.za/sites/default/files/gcis_document/201808/ippolicy2018-phasei.pdf accessed 07 October 2021.

points in DTI's Industrial Policy for Pharmaceutical industry to building investors' confidence include recommendations such as:[483]

- using government procurement to leverage local manufacturing;
- exploring the means (also political) to boost exports; and
- adopting a reasonable approach to the medicines pricing policy.

The Sub-Saharan African region needs to grow its domestic manufacturing capacity of generic ARVs by creating arrangements for transfer of technology, investment incentives, tariff protection, expedited regulatory approval processes and participation in the global pharmaceutical manufacturing world.[484]

It is submitted that an increase in pharmaceutical manufacturing will benefit South Africa in different ways, including the promotion of access to, and availability of much needed safe and effective ARVs. In Nigeria, for example, regulations permit local drug manufacturers to also be drug importers, whereas many of the leading local drug manufacturers are also representatives of global drug originators with a strong incentive to invest in local drug registration and the introduction of lucrative new products. [485] That said, few markets in Africa are as potentially lucrative as Nigeria.

However, although acknowledging that the western model of specialist physician management and advanced laboratory monitoring is not feasible in settings beset by poor resources,[486] the issue of the efficacy and safety of the ARV drugs for South African patients still require closer attention on other platforms other than those IP regulations.

3.10.5 Pricing issues

Competition over medicines pricing should be controlled through policy and legislation to improve on public access to health care, whilst complying with fair international instruments and policies. Price control is managed through different processes, one

---

483 National Department of Trade and Industry: Directorate: Pharmaceuticals and Medical Devices (28 June 2017). Overview of the South African Pharmaceuticals Industry. Portfolio Committee on Economic Development and the DTI's involvement in the State's procurement of ARV's. http://www.sapcconference.za.org/wp-content/uploads/2019/12/Gillian-Christians.pdf accessed 07 October 2021).

484 National Department of Trade and Industry: Directorate: Pharmaceuticals and Medical Devices (28 June 2017). Overview of the South African Pharmaceuticals Industry.

485 Conway, M *et al*, 'Should Sub-Sahara Africa make its own drugs?' https://www.mckinsey.com/industries/public-and-social-sector/our-insights/should-sub-saharan-africa-make-its-own-drug (accessed 28 October 2022).

486 Limited resources negatively affect affordability in South Africa regarding ARVs. CF Gilks, *et al***,** **'**The WHO Public-Health Approach to Antiretroviral Treatment against HIV in Resource-Limited Settings' (2006) 368 Lancet 505-510.

being a Pricing Committee which is appointed by the Minister of Health in terms of section 22G of the MRSA. The Pricing Committee has the authority to recommend to the Minister to regulate the introduction of a pricing system that is transparent for all scheduled substances and sold in the Republic of South Africa. In addition, the purpose of pharmaco-economic evaluations provided for in the *Regulations relating to a transparent system for medicines and scheduled substances: Guidelines for pharmacoeconomic submissions* of 2013,[487] seeks to establish whether a medicine represents fair value for money, amongst others. The objectives of these guidelines for pharmacoeconomic evaluation of new and existing medicines in the South African private healthcare sector are to create a standard for conducting economic evaluation; describe a process of compiling a submission; and promote transparency regarding the value of medicines, amongst others.

One progressive step in the right direction was when the Pharmacy Council gazetted the requirements of the Pharmacist-Initiated Management of Antiretroviral Therapy (PIMART) initiative, which proposed that pharmacists should be allowed to manage patients for ARV treatment, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) to increase access by the public to health services. The council held that the role of pharmacists would be to provide first-line treatment in line with the Health Department's approved primary health-care guidelines.[488] This initiative should be welcomed as an effort towards promoting the PLWH's access.

3.11 Conclusion

The focus of this chapter was the affordability of ARVs in the context of the right to access health care services for PLWH in South Africa. This necessitated an investigation of the regulation of IP as this relates to the development and manufacturing of ARVs, specifically pharmaceutical patents.

This chapter has alluded to some of the complexities of the IPR framework that impact on the right to access health care services, including access to ARVs in South Africa generally. In contrast to the brave strides taken by the South African government regarding ARV patents, including the management of HIV and the curbing of the virus after the Mbeki period, the road to improving access to ARVs has not been smooth and much still needs to be done. The main conclusion drawn from the discussion in the chapter is that the tension between the protection of IP on the one hand, and the

487 Government Gazette 36118, GN 68 of 1 February 2013.

488 Government Gazette 44305, Board Notice 17, of 22 March 2021. At the time of writing of the thesis, no further action was taken in this regard.

protection of public health, including access to health care services on the other, requires a careful balancing act and collaboration on multiple levels. The right to access health care services should take priority over patent protection, which should not come at the expense of people's lives. Patent laws in South Africa should be better balanced with patent protection for the right of PLWH to access medicines. Moreover, the South African government should commit to improve patient access through expanded availability through enhanced access strategies and multi-sectoral and international partnerships.

Pharmaceutical manufacturers often devote time and money to analyse the inventions of their competitors to determine whether they can produce similar products with similar effects, by doing without one of the essential features that defines the scope of patent protection. In this manner, a company can piggyback on the research of a competitor without investing the same time and resources.

As stated earlier in this thesis, resistance to ARVs and the development of ADRs, partly in response to the overuse of ARVs and also because of pathogens, or constantly adapting viruses, the need to examine the role of PGx in developing personalised HIV drugs is an urgent one, further discussed in the next chapter.

Chapter 4

The South African legal framework relating to HIV treatment and the development of personalised medicine

> "To the extent that for public health, the nineteenth century was the age of the sanitary engineer and the twentieth-century of the social engineer, the twenty-first century may well see the information engineer as the key public health worker." Ron L. Zimmern[489]

4.1 Introduction

The above statement resonates with the May 2008 National Patients' Rights Charter, which emphasises every citizen's right of participating in health policy development and decision-making insofar as their health is concerned.[490]

The notion of patient participation is further captured in Section 8 of the National Health Act, read together with Section 7, with the latter emphasising patient participation in addition to the required documentation of informed consent.[491] The international human rights treaties, especially those affecting health-related issues, seek to employ a right-based approach to health and explicitly obliges Member States to recognise patient rights.[492] A patient, including the treating doctor, require practical information towards an understanding of the relevant level of health care necessary for good health.[493]

Information engineering addresses information generation, use, distribution, and analysis, data and knowledge, in systems.[494] The information engineer in a public health sphere is expected to keep abreast with the new biotechnological demands and research which, among others, will reveal the patient's information on the condition as well as the required treatment to decrease or combat the illness.[495] Against the backdrop of patient information, the patient will, of necessity, provide informed consent to facilitate the health care machinery. The patient's information engineer is required to operate within the sphere of laws, regulations, policies, and ethics to safeguard the rights of patients to health care.[496]

---

489 RL Zimmern, 'Genomics and Individuals in Public Health Practice: Are we Luddites or Can we Meet the Challenge?' (2011) 33(4) Journal in Public Health 477–482.

490 Health Professions Council of South Africa Guidelines for Good Practice in The Health Care Professions National Patients' Rights Charter Booklet 3.

491 National Health Act 61 of 2003 Section 8

492 F Mahomed, *et al*, 'Establishing Good Practice for Human Rights-Based Approaches to Mental Health Care and Psychosocial Support in Kenya' (2020) 22(2) Health Human Rights 139-153.

493 https://onlinemasters.ohio.edu/blog/health-information-systems/ accessed 29 July 2022.

494 Roberts, S. Introduction to information engineering. https://www.robots.ox.ac.uk/~sjrob/Teaching/b4_intro_all.pdf accessed 17 November 2022.

495 A Bayat, 'Bioinformatics. (Science, Medicine, and the Future)' (2002) 324(7344) BMJ 1018-1022.

496 https://academic.oup.com/biostatistics/pages/About accessed 15 January 2022

In this chapter, the national legal framework relating to HIV treatment, access to health care services, as well as the development of personalised medicine are explored against the backdrop of the relevant global human rights framework. The chapter also addresses some of the legal barriers to the achievement of PGx and the envisaged personalised medicines in South Africa (as a RLMIC) after the national ARV rollout.

This chapter's central focus premises on the right of PLWH's access to health care services, which include safe and effective ARVs. This thesis argues that safe and effective ARVs should include personalised medicine (ARVs). The right of access to health care services in the Constitution inevitably draws on similar global and regional human rights guidelines and instruments. Therefore, it is necessary to first canvass these provisions in an attempt to determine to what extent a Constitutional interpretation of the right to access health care services may be enriched. The legislative rationale for the consideration of international provisions is mandated in Section 39(1) of the Constitution, which provides that:

> "[W]hen interpreting the Bill of Rights, a court, tribunal or forum- (a) must promote the values that underlie an open and democratic society based on human dignity, equality and freedom' and '(b) must consider international law." Also relevant is section 233 of the Constitution that directs that "when interpreting any legislation, every court must prefer any reasonable interpretation of the legislation that is consistent with international law over any alternative interpretation that is inconsistent with international law".[497]

Section 2.3.3 of the Constitution is also relevant insofar as it directs that, every Court's interpretation of the law should be compliant with international law above any other alternative interpretation.

4.2 The right to health care services in international law

4.2.1 International considerations relating to genomics and genetics generally

The role of the United Nations Educational, Scientific and Cultural Organisation (UNESCO), as well as the WHO in the context of genomics has been very instrumental in the drive towards PGx. Genomic research has generally taken the lead in WHO discourses.[498] Relevant international instruments and guidelines relevant to genetics and genomics research provide some limited and fragmented guidance, discussed in more detail in this chapter. Regrettably, most of these international provisions seem to focus on the abuses related to genetic and genomic research, most notably associated

---

497 See Section 31) of the Constitution of the Republic of South Africa, Act No. 108 of 16

498 World Health Organization, 'WHO's Science Council Launches Report calling for Equitable Expansion of Genomics' (12 July 2022) https://www.who.int/news/item/12-07-2022-who-s-science-council-launches-report-calling-for-equitable-expansion-of-genomics accessed 07 December 2022.

with unfair discrimination by third parties based on an individual's specific genetic disorder; stigmatisation due to disclosure of a person's genetic status, among others.

Article 6 of the UNESCO Universal Declaration on the Human Genome and Human Rights (1997) is most notable for its provision that:

> "[N]o one should be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity".[499]

The 2005[500] UNESCO Universal Declaration on Bioethics and Human Rights specifically aim at promoting fair access to scientific, medical and technological developments. The Declaration also emphasises the importance of the uninterrupted flow and fast sharing of knowledge and benefits regarding these developments, with reference to the requirements of developing countries.[501] Accordingly, the Declaration advocates for transnational research that is responsive to the host countries' needs and to the resolution of compelling worldwide health problems.[502]

In its Article 7, which outlaws stigmatisation and discrimination, the UNESCO International Declaration on Human Data (2003),[503] states that "every effort should be made to ensure that human genetic data are not used for purposes that are discriminatory or in any way that would lead to the stigmatisation of an individual, a family or a group".[504] These instruments are important normative statements that guide the establishment of international standards. Although lacking a legally binding force, the instruments should not be unappreciated and derogated. [505]

---

499 'Universal Declaration on the Human Genome and Human Rights' (11 November 1997) https://en.unesco.org/themes/ethics-science-and-technology/human-genome-and-human-rights accessed 23 November 2022).

500 https://en.unesco.org/about-us/legal-affairs/universal-declaration-bioethics-and-human-rights , accessed 22 November 2022.

501 Article 2(f). See also Article 15.

502 Article 21(3).

503 https://www.unesco.org/en/legal-affairs/international-declaration-human-genetic-data accessed 23 November 2022.

504 Adèle Langlois, 'The UNESCO Bioethics Programme' (2014) 20(1) The New Bioethics 3-11.

505 However, derogation is only exempted in terms of Article 4 of the ICCPR, which states: "In a time of public emergency which threatens the life of the nation and the existence of which is officially proclaimed, the States Parties to the present Covenant may take measures derogating from their obligations under the present Covenant to the extent strictly required by the exigencies of the situation, provided that such measures are not inconsistent with their other obligations under international law and do not involve discrimination solely on the ground of race, colour, sex, language, religion or social origin."

Specific to the African context, pharmacogenomics research brings high promise in the context of high genetic variability,[506] the existing high HIV burden [507] and the increase in non-communicable disease incidences.[508] The recent whole genome sequencing of hundreds of people from across Africa revealed an unexpectedly large number of new single-nucleotide variants. However, Africans comprise less than a quarter of participants in current genomics and pharmacogenomics research.[509] The need for more inclusive genetic and genomic research cannot enough be emphasised, pointing to a very unique role for the recognition and implementation of PGx on the African continent generally.

4.2.2 The Universal Declaration of Human Rights (1948)

The Universal declaration of Human Rights (UDHR)[510] serves as the incipient instrument for the observance of human rights, which includes the right to a standard of living that is proportionate to the health and access to medical care by the individual and his household. Article 25(1) provides as follows:

> "Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control."

The right to a standard of living that is adequate, is clearly articulated in Article 15 of the UDHR, which further makes references to everyone's right to security in situations of sickness. International human rights law to health care bolsters the South African government's mandate regarding the provision of medical care in diagnosing and treating diseases.[511]

4.2.3 The United Nations International Covenant on Economic, Social and Cultural Rights (ICESCR) (1966)

The realisation of a right to access health care services[512] is one of the rights that directly address patient care in the respect of human rights and is catered for in the

---

506 MC Campbell and SA Tishkoff, 'African Genetic Diversity: Implications for Human Demographic History, Modern Human Origins, and Complex Disease Mapping' (2008) 9(1) Annu Rev Genomics Hum Genet 403-433.

507 https://www.avert.org/global-hiv-and-aids-statistics accessed 15 January 2022.

508 D Tavonga, *et al*, 'Emerging Role of Pharmacogenomics in HIV Research in Africa' (2021) 16(5) Future Virology 307-310.

509 SC Schuster, *et al*, 'Complete Khoisan and Bantu Genomes from Southern Africa' (2010) 463(7283) Nature 943-947.

510 The Universal Declaration of Human Rights, ratified on the 10th December 1948.

511 Eleanor Kinney, 'The International Human Right to Health: What does this mean to the Nation and the World?' (2000) 34(1) Ind L Rev 1457.

512 The ICESCR was signed on 03 October 1994 and ratified on 12 January 2015.

International Covenant on Economic, Social and Cultural Rights (ICESCR).[513] It has been argued that HIV should be regarded as a "minimum core" threat to public health.[514] The United Nation's Committee on Economic, Social and Cultural Rights invokes the concept of 'minimum core obligations' to address the notion of the 'progressive realisation', stipulated in the ICESCR and adopted in section 27(2) the Constitution.[515] Therefore, in its General Comment 3, the Committee argued that "a minimum core obligation to ensure the satisfaction of, at the very least, minimum essential levels of each of the rights is incumbent upon every State Party." [516]

In relation to Section 231(2) of the Constitution, the ICESCR ought to be approved by Parliament through a ratification resolution in the National Assembly and the National Council of Provinces before it becomes legally binding upon the Republic. I submit that this long-winded process is not cogent with the prescript of "minimum core" in a situation where the delayed implementation of PGx will hold personalised medicine hostage. The right of accessing health care services is an immediate requirement which is in line with transformative constitutionalism, which responds to pressing societal requirements, such as the HIV pandemic.[517] Making minimum core demands justiciable is an extension of State duty and obligations to PLWH. It is also submitted that treatment for HIV and its corollary diseases presents as an emergency[518] and should be considered on a non-discrimination basis. The ICESCR recognises "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health",[519] which relates to a broad definition of health that is not limited to physical health only.

4.2.4 Convention on the Elimination of All Forms of Discrimination against Women

As alluded to earlier, HIV affects women in a disparate manner. As a result of gender discrimination and inequality, women are more severely affected by HIV than men.

---

513 ICESCR was signed on 03 October 1994 and ratified on 12 January 2015

514 Virashmee Ramdial 'A Minimum Core Content to The Right to Health for HIV Positive Persons Under South Africa's Transformative Constitution' (LLM thesis, University of Kwa-Zulu Natal 2014).

515 Virashmee Ramdial 'A Minimum Core Content to The Right to Health for HIV Positive Persons Under South Africa's Transformative Constitution' (LLM thesis, University of Kwa-Zulu Natal 2014).

516 The Minimum Core Obligations of Economic, Social and Cultural Rights: The Rights to Health and Education Dr Kirsteen Shields Research Summary | October 2017 The Nordic Trust Fund The World Bank.

517 Virashmee Ramdial 'A Minimum Core Content to The Right to Health for HIV Positive Persons Under South Africa's Transformative Constitution' (LLM thesis, University of Kwa-Zulu Natal 2014).

518 David Railton, 'What is acute HIV infection?' (PhD 2020) https://www.medicalnewstoday.com/articles/316329 accessed 11 January 2022.

519 United Nations General Assembly, International Covenant on Economic, Social and Cultural Rights, 16 December 1966.

The Convention on the Elimination of All Forms of Discrimination against Women (CEDAW) explicitly recognises sexual and reproductive rights as human rights, as do most recent HIV documents on women's human rights.[520]The preamble of the CEDAW refers and acknowledges the existence of a patriarchal structure within health care and the extensive resultant discrimination of women. The convention emphasised that such discrimination is an infraction on the right to equality and human dignity.[521] Additionally, Article 12 of the afore-cited Convention stipulates that on the basis and issue of equality between women and men, policymakers ought to implement reasonable measures in providing access to healthcare services.[522] The discrimination of women in health care is rationally and morally unjustifiable and should be eliminated.

The CEDAW Committee has often raised concerns regarding the increasing HIV/AIDS infection rates of women and girls.[523] To respond to this problem, it is recommended that countries should study the factors causing the increase in HIV infection with the aim of developing appropriate strategies to address this phenomenon and reduce women's vulnerability to the virus.

4.2.5 United Nations Convention on the Rights of the Child

Section 28(1)(c) of the Constitution[524] of the Republic of South Africa provides for the right of all children to access basic health care services, which is furthermore reinforced in national legislation through Section 13 of the Children's Act, which accentuates the following:[525]

> "(1) Every child has the right to –
> (a) have access to information on health promotion and the prevention and treatment of ill-health and disease, sexuality and reproduction;
> (b) have access to information regarding his or her health status;
> (c) have access to information regarding the causes and treatment of his or her confidentiality regarding his or her health status and the health status of a parent, care-giver or family member, except when maintaining such confidentiality is not in the best interests of the child.
> (2) Information provided to children in terms of this subsection must be relevant and health status must be in a format accessible to children, giving due consideration to the needs of disabled children.

---

520 Margaret Bamford, *Work and Health: An Introduction to Occupational Health Care* (Springer Science + Business Media BV 1995) 55.

521 United Nations Committee on the Elimination of Discrimination Against Women (CEDAW), 1992, A/47/38. http://www.refworld.org/docid/453882a422.html accessed 02 December 2021.

522 United Nations Committee on the Elimination of Discrimination Against Women (CEDAW), 1992, A/47/38. http://www.refworld.org/docid/453882a422.html accessed 02 December 2021. American Civil Liberties Union (ACLU). National Women's Law Center. CEDAW promotes women's health. https://www.aclu.org/sites/default/files/field_document/CEDAW_and_HEALTHY_WOMEN-_October_2010.pdf#:~ :text= CEDAW 20discrimination%20 againstwomen%20in,contacting accessed 22 November 2022.

524 Constitution of the Republic of South Africa, 1996.

525 Children's Act 35 of 2005, Sections 13.

(3) No person may disclose the fact that a child is HIV-positive without consent
(a) within the scope of that person's powers and duties in terms of this Act or any other law;
(b) when necessary for the purpose of carrying out the provisions of this Act;
(c) for the purpose of legal proceedings; or given in terms of subsection (2), except-15(a) in terms of an order of a court. 20(2) Consent to disclose the fact that a child is HIV-positive may be given by –
(a) the child, if the child is-(i) 12 years of age or older; or(ii) under the age of 12 years and is of sufficient maturity to understand the
(4) the parent or care-giver, if the child is under the age of 12 years and is not of sufficient maturity to understand the benefits, risks and social implications of such a disclosure.

Meanwhile, Article 24 of the Convention on the Rights of the Child provides that:

> "States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services".[526]

The Convention provides a detailed explanation of children's rights to health care and obligations of governments in ensuring that the rights are complied with.[527] The principle of accessing health care services in respect of children is an inflexible Constitutional safeguard for all children. The rationale is that states should facilitate the protection of access to a child's health information, including a child's HIV status without concern. The protection includes a prohibition against adverse inferences. The protection has a bearing on the consideration of PGx for purposes of personalised medicine as a response to ADRs, which necessitates a legitimate reason for the drawing of genetic information.

4.2.6 Declaration of Alma-Ata (1978) and related WHO policies

The Alma-Ata Declaration of 1978[528] was the precursor for Target 3.8 of the Sustainable Development Goals (SDG) for achieving universal health coverage for all people, including those in the rural areas. As a profound human right, health is also enshrined in the 2015 WHO *"Treat all"* policy. The adoption of this policy in all health facilities around the world that deal with HIV patients was strongly encouraged. The policy's recommendation to immediately treat all patients who have the HIV infection has been put into practice almost immediately in a vast majority of testing and treatment centres across the world, becoming a standard-of-care practice. Regrettably, many countries are still grappling with the notion of making health care

526 United Nations General Assembly, 'Convention on the Rights of the Child ' (United Nations, Treaty Series, vol. 1577, 20 November 1989) http://www.refworld.org/docid/3ae6b38f0.html accessed 02 December 2021.

527 https://www.unicef.org/child-rights-convention/convention-text-childrens-version accessed 02 December 2021.

528 World Health Organisation. 'International Conference on Primary Health Care' (1978) 32(11) Declaration of Alma-Ata 428-430.

accessible to all their subjects.[529] Many of the Treat All policy recommendations are now contained in the updated consolidated guidelines on HIV prevention, published by the WHO in 2021, titled: *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach*.[530]

The Alma-Ata, which proposed the year 2000 for achieving its objectives, served to preserve not only the integrity of many countries but coerce states to make a better effort in their attainment of the SDG goal of Health for All.[531] The SDGs will become compromised when states are reluctant to give effect to health interventions in line with the SDGs, such as pursuing PGx. The excuse of affordability (or fiscal difficulties) is often a response for the inability to implement, as observed by the Alma-Ata conference at the time.

The Alma Ata's legacy and main contribution is its affirmation of health care as a basic human right, whose fulfilment leads to the "attainment of the highest level of world-wide social goal".[532]

4.2.7 The UN Sustainable Development Goals and Millennium Development Goals

The MDGs were the predecessor of the SDGs developments which replaced MDGs in 2015, *inter alia*, on the issues of health care. Member States unanimously adopted the Millennium Declaration at the Millennium Summit in September 2000 at UN Headquarters in New York. The Summit led to the elaboration of eight Millennium Development Goals (MDGs) to reduce extreme poverty by 2015. With the MDGs target date reached, UN General Assembly began the negotiation process on the post-2015 development agenda in January 2015. The process culminated in the subsequent adoption of the 2030 Agenda for Sustainable Development, with 17 SDGs at its core, at the UN Sustainable Development Summit in September 2015.

The statistics on accessing health care services and the reasons for the failures to achieve the objectives of the MDGs as presented in the World Bank's Report are appalling. The extent of pre-mature death and ill-health in the developing world is staggering. In 2000 almost 11 million children died before their 5th birthday, an

529 Who HIV Policy Adoption And Implementation Status In Countries Fact Sheet JULY 2019

530 World Health Organization, (July 2021) https://www.who.int/publications/i/item/9789240031593 accessed 22 November 2022.

531 https://www.who.int/teams/social-determinants-of-health/declaration-of-alma-ata accessed 02 December 2021.

532 Declaration of Alma-Ata, International Conference on Primary Health Care, Alma-Ata, USSR, September 1978.

estimated 140 million children under 5 are underweight while 300000died from HIV/AIDS.[533] In a report published by the World Bank, Wagstaff and Claeson provide an overview of the overwhelming challenges that plague the world on health care issues.[534] The statistics regarding pre-mature death and ill-health in the developing world are staggering. In 2000 alone, almost 11 million children died before their 5th birthday, whilst an estimated 140 million children under the age of 5 are underweight.[535]

The MDGs have helped to illuminate the heightened failure in the attainment of health goals. The 2022 UN Sustainable Development Goals report is dominated by the impact of Covid-19 on health systems. The pandemic has severely disrupted health systems and essential health services, leading to disruptions across all major areas of health, including maternal and child health, immunization, mental health programmes, and treatment of diseases such as HIV, hepatitis, TB and malaria.[536]

4.2.8 UN Declaration of Commitment on HIV/AIDS Declaration of Commitment on HIV/AIDS

United Nations Declaration of Commitment on HIV/AIDS is an assembly of international governmental representatives who coined an agreement on the eventual eradication of HIV/AIDS by their respective governments. For the purposes of this study, Articles 24, 25 and 26 were deemed as relevant. Respectively, these Articles provide the following: [537]

> "24. Recognizing also that the cost, availability and affordability of drugs and related technology are significant factors to be reviewed and addressed in all aspects and that there is a need to reduce the cost of these drugs and technologies in close collaboration with the private sector and pharmaceutical companies;
>
> 25. Acknowledging that the lack of affordable pharmaceuticals and of feasible supply structures and health systems continues to hinder an effective response to HIV/AIDS in many countries, especially for the poorest people, and recalling efforts to make drugs available at low prices for those in need;
>
> 26. Welcoming the efforts of countries to promote innovation and the development of domestic industries consistent with international law in order to increase access to medicines to protect the health of their populations, and noting that the impact

533 Adam Wagstaff and Mariam Claeson, 'The Millennium Development Goals for Health Rising to the Challenge' (World Bank 2004.) https://openknowledge.worldbank.org/handle/10986/14954 accessed 07 December 2022.

534 Adam Wagstaff and Mariam Claeson, 'The Millennium Development Goals for Health Rising to the Challenge' (World Bank 2004.) https://openknowledge.worldbank.org/handle/10986/14954 accessed 07 December 2022.

535 Adam Wagstaff and Mariam Claeson, 'The Millennium Development Goals for Health Rising to the Challenge' (World Bank 2004.) https://openknowledge.worldbank.org/handle/10986/14954 accessed 07 December 2022.

536 UN Sustainable Development Goals Report (2022) https://unstats.un.org/sdgs/report/2022/The-Sustainable-Development-Goals-Report-2022.pdf accessed 22 November 2022.

537 United Nations General Assembly Resolution S-26/2 of 27 June 2001.

> of international trade agreements on access to or local manufacturing of essential drugs and on the development of new drugs needs to be evaluated further […].”

The proponents realised the need for a head-on address against coercive State practice towards HIV/AIDS. Article 24 is of paramount value, which if applied, will enhance quality access to health care services in the sense that although PGx and its off spin in the form of personalised medicine may eventually be accommodated in the technologies of drug manufacturing, the possibility of drastically reducing ADRs will eventually be realised.

The United Nations Declaration of Commitment on HIV/AIDS is a useful and effective tool which provides guidelines for preventing HIV/AIDS infections, and a review of budgetary concerns as well as the promotion of access to treatment for all the PLWH. The vision for the Assembly was the drive for an effective response to HIV/AIDS and the realisation of human rights and fundamental freedoms for all.

4.3 The right of access to health care services in regional instruments

The United Nation’s Universal Declaration on Human Rights was instrumental in the formation of the African Charter on Human and Peoples’ Rights on the African continent.[538] The Charter is the principal instrument for the promotion and protection of human and peoples’ rights. Article 16 is a replica of Article 25 of the UDHR on issues of the enjoyment of the right to accessing health and access to medical attention for all the peoples of the African continent.[539]

4.3.1 African Charter on Human and People’s Rights

The African Charter on Human and People’s rights is a crucial regional human rights tool on a continent where HIV is rampant. The object of Article 16 of the Charter is weighty in that it assures the individual that State Parties shall “take the necessary measures to protect the health of their people and ensure that they receive medical attention when sick.”[540]

The State Parties need to give effect to the Charter’s obligation of ensuring that medical attention is provided to the sick, including PLWH. One such medical

---

538 Organization of African Unity, African Charter on Human and People's Rights (Banjul Charter 27 June 1981).

539 Article 16
1. Every individual shall have the right to enjoy the best attainable state of physical and mental health.
2. States parties to the present Charter shall take the necessary measures to protect the health of their people and to ensure that they receive medical attention when they are sick.

540 Organization of African Unity, African Charter on Human and People's Rights (Banjul Charter 27 June 1981).

intervention should of necessity include safe and efficacious ARVs for the states' subjects, which is achievable with the application of PGx in the development of personalised ARVs.

The South African government, by virtue of the fact that it signed the charter on 10 October 1997 and deposited its Instrument of Accession on 21 January 2001, are obliged to actualise the Charter's provisions by taking the requisite steps (prioritise PGx) for protecting its people's health, specifically the most vulnerable, which include PLWH (by developing personalised ARVs/ART), who continue to suffer severely from ADRs relating to their HIV treatment.

4.3.2 The Constitutive Act of the African Union

South Africa is the 53rd African country to attain political independence, therefore, it is bound by the legal instruments such as the African Union's Constitutive Act. A marked progress in addressing the multiple challenges of HIV and AIDS in the country is more visible than before. The commitment made by the South African government, both to the regional[541] and international conventions and assemblies, has made reducing the HIV burden, as well as treating PLWH with the safest and most effective ARVs, a priority in the quest to protect the PLWH's human rights.

Article 3 of the African Union's Consultative Act further strengthens the role of the South African government's commitment towards the promotion of human rights.[542] Irrespective of the protection of human rights, of which the right of access to health care services is paramount, ADRs relating to HIV treatment remain a Sword of Damocles ready, to thwart the objective of ARVs, making the implementation of PGx and personalised medicine more critical than ever before.[543]

4.3.3 Protocol to the African Charter on the Rights of Women (2003)

The Protocol to the African Charter on the Rights of Women[544] was adopted in Maputo, on 01 July 2003. However, it took two more years to put it into effect. Causing the

---

541 SADC HIV and AIDS framework 2010 – 2015.

542 Article 3 of the Constitutive Act of the African Union provides that the union intends on "promoting and protecting human and peoples' rights in accordance with the African Charter on Human and Peoples' Rights and other relevant human rights instruments and to work with relevan international partners in the eradication of preventable diseases and the promotion of good health on the continent

543 http://www.africa-union.org/root/au/AboutAu/Constitutive_Act_en.htm accessed 03 December 2021.

544 Protocol to the African Charter on the Rights of Women, adopted by the 2nd Ordinary Session of the Assembly of the Union Maputo, Mozambique, 11th July 2003. Entry into Force: 25th November 2005. https://au.int/en/treaties/protocol-african-charter-human-and-peoples-rights-rights-women-africa (accessed 22 November 2022).

delay in the implementation was that the protocol addresses the historical principle of patriarchy exercised, as well as the utilitarian necessity of the African culture.[545] Therefore, most State Parties took some time to ratify the protocol, while Article 18 of the African Charter on Human and Peoples' Rights lends itself to other international declarations and conventions concerned with eliminating every form of discrimination against women and ensures the protection of women's rights.[546] In its proactive endeavour to protect children's and women's rights, the United Nations played a pivotal role with an impetus in the formation of a catalyst to encourage the protection.[547]

The affirmation of equality between men and women is enshrined in Articles 2 and 8 of the Constitutive Act of the African Union and call for African States to recognise the importance of women and men as partners who are equal in the development of Africa.[548] As such, Article 14 of the Protocol to the African Charter on the Rights of Women provides the due process mechanism as a standard which State Parties, as international bodies, can rely on to ''ensure that the right to health of women, including sexual and reproductive health is respected and promoted".[549]

4.3.4 The African Charter on the Rights and Welfare of the Child (1990)

Children are synonymous with vulnerability. Most African children are connected to suffering brought about by power and political desperation. An additional woe to the children of Africa, despite that Article 14(2)(d) of the African Charter on the Rights and Welfare of the Child[550] promotes the provision of the required health care and medical assistance to every child, with specific emphasis on developing primary health care PHC) and to thwart malnutrition and diseases within the PHC framework by applying relevant technology.[551] The latter assertion is viewed as the plight of ADRs that

---

545 Senyonjo and Manisuli, 'Culture and the Human Rights of Women in Africa: Between Light and Shadow' (2007) 51(1) Journal of African Law 39–67.

546 Article 18 of the African Charter on Human and Peoples' Rights calls on all State Parties to eliminate every discrimination against women and to ensure the protection of the rights of women as stipulated in international declarations and conventions.

547 UN Women Strategic Plan, the United Nations General Assembly created UN Women in July 2010.

548 P Koffi Kounte Protocol to the African Charter on Human and People's Rights on The Rights of Women In Africa. (Simplified) WiLDAF-West Africa Women in Law and Development in Africa

549 http://www.achpr.org/files/instruments/women-protocol/achpr_instr_proto_women_eng.pdf accessed 03 December 2021.

550 African Union. Adopted by by the 26th Ordinary Session of the Assembly of Heads of State and Government of the OAU Addis Ababa, Ethiopia, (29 November 1999) https://au.int/sites/default/files/treaties/36804-treaty-african_charter_on_rights_welfare_of_the_child.pdf accessed 22 November 2022.

551 https://au.int/en/treaties/african-charter-rights-and-welfare-child accessed 03 December 2021.

accompany ARVs provided to children, and have been developed by pharmaceutical companies predominantly from high-income countries.

Regrettably Singhal and Howard,[552] report that some State Parties refuse to live up to the obligations and responsibilities espoused by the relevant conventions and assemblies they had signed towards promoting the protection of children.[553]

4.4 Selected legal and policy considerations

The potential of PGx and the development of personalised medicine have already been explored by local researchers.[554] Once agreement is reached in South Africa on the importance of PGx in the development of safe and effective ARVs, the legislature, scientists and drug manufacturers could consider proceeding with the three-fold approach to implementation of PGx, namely:

(i) to use patient demographics to determine the race of the patient and match existing information from the Human Genome Project (HGP);[555]
(ii) to use the Health Technology Assessment (HTA) on the patient's DNA to determine susceptibility to ADRs towards a particular medicine; [556] and,
(iii) to proceed with the manufacturing of and the introduction of prescription medicines that are more compatible to patients.[557]

The implementation of PGx in South African will need to address the lack of training on the part of those who need to coordinate the systemic administration and application of medicines.[558] The National Health Insurance Policy of 2017[559] rightly identifies as one of the obstacles relating to Health Technology Assessment (which would include an assessment of the social, economic, organisational and ethical issues of PGx as a health intervention and health technology) the issue of "cost-

552 Arvind Singhal and W Stephen Howard, *The Children of Africa confront AIDS from vulnerability to possibility* (Ohio University Press 2003).
553 Notes for press briefing by Stephen Lewis, UN Secretary-General's Special Envoy for HIV/AIDS in Africa, on his recent trips to Malawi and Tanzania, (United Nation 18 January 2005).
554 Louise Warnich, *et al,* 'Pharmacogenomic Research in South Africa: Lesson Learned and Future Opportunities in the Rainbow Nation' (2011) 9(3) Current Pharmacogenomic and Personalized Medicine 191-207.
555 AJ Gates*, et al*, 'A Wealth of Discovery Built on the Human Genome Project — by the Numbers' (2021) 590(7845) Nature 212-215.
556 CS Goodman, 'HTA 101: Introduction to Health Technology Assessment' (Bethesda MD: National Library of Medicine (US) 2014) https://www.nlm.nih.gov/nichsr/hta101/HTA_101_FINAL_7-23-14.pdf accessed 07 December 2022.
557 'Health Harnessing the Power of Precision Medicine' (Editorial Staff UCSF Magazine Fall 2013) https://magazine.ucsf.edu/harnessing-power-precision-medicine accessed 19 July 2022.
558 PJ Caraballo, *et al,* 'Multidisciplinary Model to Implement Pharmacogenomics at the Point of Care' (2-17) 19(4) Genet Med 421-429.
559 National Health Insurance Policy, Government Gazette 40955 (GN 627) of 30 June 2017.

effectiveness and accessibility of needed interventions and priority".[560] Clause 304 of the Policy acknowledges that policy and laws are a priority to guide HTA-related resources to achieve sustainable health endeavours.[561]

It is a well-known fact that the South African public health system is seriously in need of an extensive overhaul in order to distribute health care and health resources fairly and equitably.[562] At the national level, much of attention and focus is currently on the NHI system's implementation. With the practice of HTA still in its infancy in South Africa, only time will tell when and whether PGx will be prioritised as part of the NHI's implementation, specifically considering the NHI Policy's observation that "[e]fficient use of resources is a crucial factor for achieving a sustainable health system especially when significant increase in access to essential medicines, including generic medicines, medical devices, procedures and other healthcare interventions are envisaged."[563]

Regrettably, the existing legal framework governing the removal, transplant, use and processing of human biological materials, namely chapters 8[564] and 9[565] of the National Health Act,[566] including relevant regulations, in chapters 8 and 9 serve to obscure, rather than clarify the development of a national strategy and policy towards the application of PGx,[567] as will be discussed in more detail below.

Although the NHA regulates the use of tissue, blood and blood products, or gametes withdrawn or removed from living persons,[568] it falls desperately short of providing legal clarity on current technological developments in medical science,[569] such as genetic and genomic research and gene editing. The process of amending health legislation in South Africa is a slow and cumbersome process generally.[570] The responsibility of addressing ADRs in South Africa falls within the remit of the South African Health

560 Clause 303 Of Government Gazette No. 40955, 30 JUNE 2017.
561 Clause 304 of Government Gazette No. 40955, 30 June 2017
562 Ames Dhai and David McQuoid-Mason, *Bioethics, Human Rights and Health Law Principles and Practice* (Juta 2011).
563 National Health Insurance Policy. Government Gazette 40955 (GN 627) of 30 June 2017, clause 304.
564 Section 56 (1) of Chapter 8 refers to the use of tissue, blood, blood products or gametes removed or withdrawn from living persons only for such medical or dental purposes as may be prescribed.
565 Section 69 (1) of chapter 9 alludes to the establishment of "a committee to be known as the National Health Research Committee" without making mention of how the committee should adjudicate on matters of genetic of genomic research.
566 Chapter 8 of National Health Act 61 of 2003.
567 N Ayati, *et al*, 'Pharmacogenomics Implementation and Hurdles to Overcome; In the Context of a Developing Country' (2021) 20(4) Iran Journal of Pharmaceutical Research 92-106.
568 National Health Act 61 of 2003
569 MS Pepper, 'Enactment of Chapter 8 of the National Health Act and regulations thereto' (2012) 5(1) South African Journal of Bioethics and Law.
570 MS Pepper, (2012) 5(1) South African Journal of Bioethics and Law Medical.

Products Regulatory Authority (SAHPRA), which provides guidance on the handling of ADRs.[571] The ADRs are also monitored in studies under oversight of registered research ethics committees of institutions. The NHA directs in Section 73 that all health research in South Africa should be conducted under the oversight of a research ethics committee that is registered with the National Health Research Ethics Council. The National Health Research Committee (not to be confused with the National Health Research Ethics Council) advises the Minister on the identification of health research priorities (Section 70(1)). One such priority could be the need to explore the application of PGx as part of identifying the health needs of PLWH who are severely affected by ADRs.

In advising the Minister of Health on relevant priorities for health research, the National Health Research Committee also ought to have regard to:

(a) the disease burden;
(b) the pricing of the interventions for reducing the disease burden;
(c) institutional and human resource availability for implementing an intervention within the affected communities' proximity;
(d) the health requirements of the groups at risk, such as children, women, as well as the elderly and the disabled; and
(e) the health needs of communities are still identified with the high disease burden, notwithstanding that HIV incidences are reportedly on a decline in South Africa.

It is submitted that these factors should include a focal investigation of the pricing of the interventions intended for reducing the HIV disease burden and its intermittent ADRs through PGx.

Section 1 of the National Health Act defines health research as "any research which contributes to knowledge of- (a) the biological, clinical, psychological or social processes in human beings; (b) improved methods for the provision of health services; (c) human pathology; (d) the causes of disease; (e) the effects of the environment on the human body; (f) the development or new application of pharmaceuticals, medicines and (g) the development of new applications of health technology". Accordingly, genomic and genetic research undoubtedly falls within the description of "health research", as would pharmacogenomics research specifically.

---

571 South African Health Products Regulatory Authority, 'Guidelines for Adverse Drug Reaction ADR's Reporting for Health Care Professionals' (28 March 2022) https://www.sahpra.org.za/wp-content/uploads/2020/04/ADR-Reporting-Guideline_HCPs_v1_for-commenting_March-2020.pdf accessed 07 December 2022.

The South African ART Clinical Guideline makes no reference to PGx,[572] in spite of the fact that HIV is still a burden in South Africa. Promisingly, PGx is specifically mentioned in the National Biotechnology Strategy for South Africa.[573]

One development that will hopefully assist in promoting the benefits of PGx, is the work by the Academy of Science of South Africa (ASSAf)[574] Working Group that was tasked with conducting a consensus study on the legal, ethical and social issues relating to genomics and genetics. In its 2018 report, titled, *Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications*, the working group also sets out several recommendations to address the challenges in this context.[575] Some of these recommendations will be, where relevant, refer to in this thesis.

The PGx research geared towards the development of personalised medicine will require the "extraction of large amounts of data from human tissue, for example, blood''.[576] It is for this reason that research ethics committees, when reviewing applications for ethical clearance of research protocols that will remove, use, process and transfer human biological material, as well as use and further processed the data derived from such samples as part of PGx research, be familiar with the legal requirements relevant to the regulation of human biological material, as well as the processing of personal information of research participants in accordance with relevant privacy protection legislation (discussed below).

As this chapter will discuss, the development of personalised medicine should consider, at a starting point, the Constitutional framework pertinent to any intervention (research or therapy) that concerns an individual. Section 12 of the Constitution protects a person's right to security and freedom; whereas Section 12(2)(c) extends this to the protection of the right to psychological and bodily integrity, which entails the right to be exonerated from scientific or medical experiments without their informed

---

572 ART Clinical Guideline 2019 2020

573 Louise Warnich, *et al*, 'Pharmacogenomic Research in South Africa: Lesson Learned and Future Opportunities in the Rainbow Nation' (2011) 9(3) Current Pharmacogenomic and Personalized Medicine 191-207.

574 The Parliament of South Africa passed the Academy of Science of South Africa Act 67 of 2001, which came into force on 15 May 2002.

575 ASSAf, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications' (4 December 2018) https://www.researchgate.net/publication/329220071_ASSAf_consensus_study_on_the_ethical_legal_and_social_implications_of_genetics_and_genomics_in_South_Africa accessed 17 November 2022.

576 ASSAf, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications' (4 December 2018) https://www.researchgate.net/publication/329220071_ASSAf_consensus_study_on_the_ethical_legal_and_social_implications_of_genetics_and_genomics_in_South_Africa accessed 17 November 2022

consent. Respecting bodily integrity by requiring informed consent is echoed in the National Health Act by virtue of section 7(1) which states that, subject to section 8, a health service may not be provided to a user (patient) without the user's informed consent. Section 11 of the NHA gives effect to health services for experimental or research conducted on a user, namely that a user ought to be informed if the health service is for experimental or research purposes before any experimental or research health service is provided to such user.

While PGx continues to advance at a fast pace globally, it is imperative that South Africa does not fall behind. Although the right to HIV treatment is mostly framed in the context of a right to health, which include the right to access health care services more specifically, more attention should be afforded to the violation of the rights of persons living with HIV and AIDS in the *context of patient care* and not only in the clinical and research context. Cohen and Ezer[577] rightly maintain that "[a] vast and severe range of human rights violations occur in the patient care context." Health care that includes ARVs should produce the desired effect. Human rights in the context of patient care should be recognised and where violated, enforced through judicial action.[578] Turning a blind eye to ADRs in the treatment regime of PLWH may be seen to constitute a violation of their human rights in patient care, as will be argued elsewhere in this chapter.

The obstacles faced by PLWH in accessing health care services and safe and effective ARVs have already been outlined in chapter three. This situation is compounded by a legal framework that is vague insofar as the minimum core of legal entitlements of PLWH and AIDS in the realm of health care is concerned. The question rightly arises as to whether the current situation is reconcilable with the notion of transformative constitutionalism, which requires the judiciary's development of a human rights construction that accords with the fundamental tenets of the Constitution.

Transformative constitutionalism generally means using the law to effect comprehensive social change through non-violence means. American Professor Karl Klare first described the concept of transformative constitutionalism in his work titled "Legal Culture and Transformative Constitutionalism".[579] For Klare (1988), therefore,

---

577 Jonathan Cohen and Tamar Ezer, 'Human rights in patient care: A theoretical and practical Framework' (2013) 15(2) Health and Human Rights.

578 Jonathan Cohen and Tamar Ezer, 'Human rights in patient care: A theoretical and practical Framework' (2013) 15(2) Health and Human Rights.

579 Karl E Klare, 'Legal Culture and Transformative Constitutionalism' (1998) 14(1) South African Journal on Human Rights 146-188.

transformative constitutionalism is 'a long-term project of constitutional enactment, interpretation, and enforcement committed to transforming a country's political and social institutions and power relationships in a democratic, participatory, and egalitarian direction'[580]

The right of access to health care services has been truncated and paraphrased to the popular notion of availability of resources. The reality is that obstacles that unjustifiably impede the access of PLWH to *safe and effective* health care services also have dire consequences for the right to life of PLWH. The primary question arising thus is how South Africa may overcome resource constraints or other factors impacting on progressive realisation of the right to accessing health care services, which encompasses access to safe and effective HIV treatment, informed and based on an application of pharmacogenomics.

4.5 Legal framework governing access to health care services and personalised medicine

The Constitution of the Republic of South Africa, Act No. 108 of1996 is at the apex of the South African legal framework on the right of PLAW to safe and effective health care services (personalised ARV medicines). Section 27(1)[581] of the Constitution entrenches the right of access to health care services.

Meanwhile, Section 39(1) of the Constitution directs that the Courts are bound to consider international law when rights are interpreted. This provision will become meaningful when an argument as to the right of PLWH to have access to health care services (which imply safe and effective services) is interpreted, as consideration could be given to relevant international human rights instruments that may guide a court's interpretation of Section 27(1).

4.5.1 Right of access to health care services (section 27(1))

For the purpose of this discussion, an interpretation of the above right will also consider relevant Constitutional jurisprudence relating to the rights of PLWH. The right of access in Section 27 applies to both health care services and access to food, water, and social

---

580 Karl E Klare, 'Legal Culture and Transformative Constitutionalism' (1998) 14(1) South African Journal on Human Rights 146-188.

581 Section 27 of the Constitution. Health care, food, water and social security.

1. Everyone has the right to have access to - health care services, including reproductive health care; sufficient food and water; and social security, including, if they are unable to support themselves and their dependants, appropriate social assistance.
2. The State ought to take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of each of these rights.
3. No one may be refused emergency medical treatment.

security. Of great concern is the limitation embedded in Sub-section 2 of Section 27, which provides that "the State must take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of each of these rights." South Africa's health care system is deeply inequitable, with a limping public health system on the one hand, and a financially motivated private health system on the other. Needless to mention, most of South Africa's indigent population have to rely on the public health system.[582]

Section 27[583] is highly influenced by Article 25(1) of the UDHR,[584] which includes a wide range of rights, including those to adequate food, water, sanitation, clothing, housing, and medical care, as well as social protection for situations beyond a person's control, such as disability, widowhood, unemployment and old age. Article 25 does not contain an inherent limitation, whereas Section 27(2) of the South African Constitution leaves the fulfilment of the right dependent on the availability or lack of resources.

Two landmark cases that tested the legitimacy of the limitation embedded in Section 27 are very important for the purpose of this chapter.

4.5.1.1 Soobramoney v Minister of Health, KwaZulu-Natal

The first is the case of *Soobramoney v Minister of Health, KwaZulu-Natal*.[585] In this case, the Constitutional Court found that the duty placed on the State in terms of Section 27(2) depends on the "means available for such purpose" which conveys an inherent limitation on account of lack of means. Section 27(3), which provides that "no one may be refused emergency medical treatment", was interpreted by the Constitutional Court "not to include ongoing treatment of chronic diseases that prolongs life.''[586] Section 27(3) is of particular importance for Mr Soobramoney, who brought an application to the Durban High Court for an order that the Addington hospital provides him with life-saving dialysis treatment, citing Section 27(3) and Section 11 of the Constitution (the latter protecting the right to life).

The court's understanding of "emergency medical treatment''[587] is elusive and difficult to accept. It is submitted that the mandate to give a definition of the concept resides

582 E Kramer, 'No one may be Refused Emergency Medical Treatment' - Ethical Dilemmas in South African Emergency Medicine' (2008) 1(2) South African Journal of Bioethics and Law 53-56.

583 The Constitution of the Republic South Africa, 1996. Section 27(1) Everyone has the right to have access to health care services, including reproductive health care.

584 Article 25(1).

585 *Soobramoney v Minister of Health, KwaZulu Natal* 1998 (1) 756 (CC).

586 *Soobramoney v Minister of Health, KwaZulu Natal* 1998 (1) 756 (CC).

587 *Soobramoney v Minister of Health, KwaZulu Natal* 1998 (1) 756 (CC).

within the domain of medical fraternity, and not the legal profession, whose involvement in a medical case happens *ex-post facto*. A treating medical professional carries the responsibility to redefine what constitutes an appropriate definition of a ‘’medical emergency” in modern-day South Africa for purposes of Section 27(3)’.[588]

To the extent that HIV is currently being treated in terms of the available resources without an eminent cure. However, there remains the challenge of ADRs which are exacerbated by chronicity.[589] The relevance of Section 27 for PLWH suffering from ADRs because of their HIV treatment may possibly be found in a progressive reading of Section 27(1), which guarantees the right to have access to “health care services”. It is interesting that the NHA does not refer to “health care services”, but “health services”. “Health services” is defined in the NHA as “(a) health care services, including reproductive health care and emergency medical treatment, contemplated in Section 27 of the Constitution; (b) basic nutrition and basic health care services contemplated in Section 28(l)(c) of the Constitution; (c) medical treatment contemplated in Section 35(2)(e) of the Constitution; and (d) municipal health services”. This definition includes medical treatment for PLWH, which should not only comply with relevant standards of care in clinical practice, but also reflect the objectives of the National Drug Policy (NDP), in which the government of South Africa clearly outlines its commitment to ensuring availability and accessibility of medicines for all people, which include “to ensure the availability and accessibility of essential medicines to all citizens” and “to ensure the safety, efficacy and quality of drugs.”[590] PLWH are therefore have the right to have access to safe and effective ARVs, based on a reading of Section 27(1), together with the NDP.

4.5.1.2 Minister of Health v Treatment Action Campaign (TAC)

In matter of the *Minister of Health v Treatment Action Campaign (TAC),*[591] the applicants sought an order that the respondents (the Minister of Health and others) make Nevirapine available to pregnant women with HIV giving birth in public health institutions and “produce and implement an effective national programme to prevent or reduce mother to child transmission (MTCT) of HIV, including the provision of voluntary counselling and testing (VCT) and, where appropriate, Nevirapine, or other appropriate medicine, as well as formula milk for feeding.” The respondents had made

588 E Kramer, (2008) 1(2) South African Journal of Bioethics & Law 53-56.
589 CJ Colvin, ‘HIV/AIDS, Chronic Diseases and Globalisation’ (2011) 7(31) Global Health.
590 National Drug Policy (1996). https://www.gov.za/documents/national-drugs-policy (accessed 17 November 2022).
591 *Minister of Health v Treatment Action Campaign (TAC)* 2002 (5) SALR 721 (CC).

Nevirapine available for the prevention of MTCT at a limited number of pilot sites, with the aim to test its implementation. [592] A central focus in this case was the limitation in Section 27(2), namely that the implementation of Section 27(1) is dependent on the availability of state resources, together with the state's obligation to take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of rights contained in Section 27(1).[593] As a chronic disease, treatment for HIV requires ARVs for the management of the condition.[594] PLWH include pregnant women, whose unborn children were at risk of becoming infected.

Nevirapine, as an ARV and a preventative measure against mother-to-child-transmission (MTCT), not only has the capacity to treat the HIV-positive mother, but also would allow the mother to exercise her right to have a child. Nevirapine will also prevent that such child contract HIV from the mother *in utero*, in addition to promoting the mother's right to have access to health care services.[595]

The TAC's main objective was to compel health authorities to implement an effective national programme to prevent or reduce MTCT of HIV. In the *Soobramoney* case, the applicant relied on the concept of "everyone" as stated in Section 27(1), also invoking the right to emergency medical treatment in Section 27(3). The interpretation of Section 27(2) in both cases played out differently: in *Soobramoney*, affordability, specifically the lack of available resources was successfully relied upon by the state, whereas in the *TAC* matter, the government relented and supplied the required treatment to pregnant women. So, despite applicants in both cases relying on the provisions of sub-Section 27(1) and Sub-section 27(3), different outcomes resulted.

The High Court in the TAC matter concluded by giving due recognition to the protection afforded by Section 27 of the Constitution, whilst the government was scrambling to find a legal and constitutional justification for the refusal of granting a countrywide prevention programme of Nevirapine. The High Court found that the government had not taken reasonable steps to address the need to reduce mother-to-child transmission of HIV and ordered the government to develop a comprehensive programme to make Nevirapine available in public health facilities. The Government appealed.

---

592 *Minister of Health v Treatment Action Campaign (TAC)* 2002 (5) SALR 721 (CC) [16].

593 David Bilchitz, 'South Africa: Right to health and access to HIV/AIDS drug treatment' (2003) 3(1) International Journal of Constitutional Law, 524-534.

594 Kathy Katella, 'How HIV Became the Virus We Can Treat' (Yale Medicine, 12 October 2021) https://www.yalemedicine.org/news/hiv-treatable accessed 07 December 2022.

595 http://kelinkenya.org/wp-content/uploads/2010/10/Treatment-Action-Campaing-Vs-Minister-of-Health.pdf accessed 07 January 2022.

It is thus clear that the provision of treatment to PLWH is an ineluctable obligation of the state to its subjects. The decision was confirmed by the Constitutional Court in *Minister of Health v Treatment Action Campaign (No 2)*.[596] The Court held that government policy whereby Nevirapine was available only in certain research site within the public sector was indeed inflexible and unconstitutional.

4.6 Prohibition of unfair discrimination

The milestone of the introduction of Nevirapine was followed by increased attention on women's rights and their struggle against discrimination. Despite the success in the TAC cases,[597] the TAC at the time has lamented the fact that although the equality clause (Section 9 of the Constitution) remains steadfast on equality rights, the scourge of abuse against women remains uncurbed.[598] In terms of the equality clause, the State should not directly or indirectly discriminate against a person (in this case, women) where a purposive reference is made to gender, sex and pregnancy. Furthermore, Sub-Section 4 of Section 9 furthermore provides that national legislation should be enacted to prevent or prohibit unfair discrimination.[599]

Since HIV opens a new door to discrimination and stigmatisation, genetic testing has a potential negative impact on issues of human dignity as the genetic constitution of an individual could be abused as a tool for discrimination.[600] These historically undermining circumstances have led to the development of Constitutional protection.[601] Discrimination against PLWH may perpetuate further reactionary conduct in a social sphere, which has the potential to lead to either self- or publicly perceived stigmatisation.[602] The actual or perceived repugnance by the public against

---

596 *Minister of Health v Treatment Action Campaign* (No 2) 2002 (5) SA 721 (CC).

597 https://www.tac.org.za/campaigns/gender-inequality/ accessed 08 January 2022.

598 The Constitution of the Republic of South Africa, 1996. Section 9 provides that: Everyone is equal before the law, and everyone has the right to equal protection and benefit of the law

599 Section 9(3) the State may not unfairly discriminate directly or indirectly against anyone on one or more grounds, including race, gender, sex, pregnancy, marital status, ethnic or social origin, colour, sexual orientation, age, disability, religion, conscience, belief, culture, language and birth. (4) No person may unfairly discriminate directly or indirectly against anyone on one or more grounds in terms of Sub-section 3. National legislation should be enacted to prevent or prohibit unfair discrimination.

600 Section 10: Human dignity. Everyone has inherent dignity and the right to have their dignity respected and protected. Constitution of the Republic of South Africa, 1996.

601 H Markel, 'The stigma of disease: The implications of genetic screening' (1992) 93(2) American Journal of Medicine 209-215 at 210.

602 L Yvonne, *et al,* 'Role of Self-Stigma in Pathways from HIV-Related Stigma to Quality of Life Among People Living with HIV AIDS Patient Care and STDs' (2021) 35(6) Behavioural and Psychosocial Research.

PLWH has a detrimental effect on issues of disclosure and access to treatment and undermines the efforts to prevent and treat HIV.[603]

Unfair discrimination against women with HIV is particularly harsh. Women are more vulnerable to HIV infection[604] due to the perceived traditional position of women in the society.[605] South Africa recognises the scourge of gender-based violence particularly against women and children. Gender-based violence emanates from gender inequality experienced by PLWH and particularly women.[606] A lot has already been written on stigmatisation associated with HIV and AIDS. The following explanation summarises some of the reasons of stigmatisation:

> "Stigmatization associated with AIDS is underpinned by many factors, including lack of understanding of the illness, misconceptions about how HIV is transmitted, lack of access to treatment, irresponsible media reporting on the epidemic, the incurability of AIDS, and prejudice and fears relating to a number of socially sensitive issues including sexuality, disease and death, and drug use."[607]

On World AIDS Day in 2021, Deputy President Mr Mabuza appealed for HIV treatment, care and support that is free from stigma and discrimination for all those who test positive for any of the related diseases, especially HIV and TB.[608] The struggle for HIV positive women in South Africa to manage the stigma and discrimination is real and difficult.[609] Globally, and also in South Africa, women constitute the highest number of PLWH as evidenced through the high numbers of infections among women and young girls.[610] Figures revealed by the South African National AIDS Council (SANAC) confirms that HIV prevalence among young women is nearly four times greater than that of young men - a fact that pre-supposes possible stigmatisation.[611] Unaccommodating attitudes towards women and young girls can negatively impact on their access to treatment and the ability to access health care services.[612] As mentioned already, HIV disproportionately affects women and girls because of their

---

603 MJ Visser, *et al*, 'HIV/AIDS Stigma in a South African Community' (2009) 21(2) AIDS Care 197-206.

604 T Turmen, 'Gender and HIV/AIDS' (2003) 82(3) International Journal of Gynecology and Obstetrics 411–418.

605 Maureen Mswela, 'Female genital mutilation: Medico-legal issues' (2010) 29(1) Medicine and Law 523-536.

606 https://www.hiv.gov/hiv-basics/overview/making-a-difference/standing-up-to-stigma accessed 10 January 2022.

607 https://data.unaids.org/publications/irc-pub06/jc999-humrightsviol_en.pdf. accessed 08 January 2022.

608 Deputy President David Mabuza: World AIDS Day commemoration (01 Dec 2021).

609 The World Health Organization '16 Ideas for Addressing Violence against Women in the Context of the HIV epidemic: A Programming Tool' (WHO 2013).

610 Sia Onadja, *et al,* 'What Explains Gender Inequalities in HIV/AIDS Prevalence in Sub-Saharan Africa? Evidence from the Demographic and health surveys' (2016) 16(1136) BMC Public Health.

611 Michel Sidibé, former executive director of UNAIDS.

612 2014-WAD-guidelines. https://sanac.org.za/wp-content/uploads/2018/08/2014-WAD-guidelines.pdf. accessed 08 January 2022.

unequal cultural, social and economic status in society thus portraying the notion that the HIV epidemic is attributable to women.[613]

The copious evidence of the impact of HIV/AIDS on society and the prejudice and discrimination against PLWH[614] was unfortunately further exacerbated by the South African government's denialism, discussed in chapter two of this thesis.

4.7 Privacy considerations

Current areas in which personalised approaches hold specific promise include oncology, cardiovascular diseases, neurodegenerative diseases, psychiatric disorders, diabetes and obesity, arthritis, pain, and Alzheimer's disease. The personalised medicine approach has the potential to provide better health outcomes, improved treatments, and a reduction in toxicity due to adverse drug responses.

As discussed already, the development of personalised medicine requires health information engineering to create data using an individual's genomic and genetic information to predict suitable individualised medicines.[615] Reference has already been made to the need for the protection of genetic or genomic information of individuals, which is recognised as "special personal information" in terms of the Protection of Personal Information Act.[616] The possible identification, as well as the distinctiveness of persons' individual genes, makes stigmatisation throughout the PGx enterprise highly likely. The practice of PGx exposes PLWH to possible "discrimination based on genetic characteristics,[617] which adds a further layer of possible discrimination in addition to the stigmatisation as a result of their HIV status. Such stigmatisation not only relates to an affected individual, but also a family or a group or communities."[618]

---

613 The World Health Organization '16 Ideas for Addressing Violence against Women in the Context of the HIV epidemic: A Programming Tool' (WHO 2013) https://apps.who.int/iris/handle/10665/95156 accessed 07 December 2022.

614 The Promotion of Equality and Prevention of Unfair Discrimination Act 4 of 2000, section 34.

615 KB Brothers and MA Rothstein, 'Ethical, Legal and Social Implications of Incorporating Personalized Medicine into Healthcare' (2015) 12(1) Per Med 43-51.

616 Protection of Personal Information Act 4 of 2013.

617 Section 9(3)(4) of the Constitution of the Republic of South Africa 1996 incorporates genes as an identifier, which warrants protection in the Bill of Rights. Section 9(3) the State may not unfairly discriminate directly or indirectly against anyone on one or more grounds, including race, gender, sex, pregnancy, marital status, ethnic or social origin, colour, sexual orientation, age, disability, religion, conscience, belief, culture, language and birth. (4) No person may unfairly discriminate directly or indirectly against anyone on one or more grounds in terms of subsection 3. National legislation ought to be enacted to prevent or prohibit unfair discrimination.

618 ECOSOC Resolution 2004/9 Genetic privacy and non-discrimination. See also section 14 of The Constitution of the Republic of South Africa, 1996.

The full implementation of PGx for the development of personalised medicine requires a robust legal framework that not only covers and protects the participation of PLWH in health research, but also protects PLWH in a clinical context of treatment. Such framework should also regulate the development of safe and effective medicines, which in the case of personalised medicine, should be calibrated to effectively treat a specific individual. A range of human rights of PLWH in the last-mentioned context becomes clear, including the right to bodily and psychological integrity, which includes personal autonomy, the rights to equality, human dignity and right to privacy, to name but a few.

4.7.1 Right to privacy

Genes have a propensity to expose personal as well as lineal health medical information, which may place an individual or lineage in jeopardy or at a risk of becoming stigmatised. Consent for the processing or use of personal information by a relevant individual may not always sufficiently protect a person against discriminatory practices, such as the use of the genetic data by employers, health care providers or insurance companies. It is often the use of the same personal information for purposes other than what is covered in the initial consent. Disclosure without the re-consent of the individual may infringe on the individual's right to privacy.[619]

Section 14 of the Constitution[620] protects a person's right to privacy in general terms, this also includes information relating to a person's health status and treatment.[621] In the context of HIV and AIDS, the protection of privacy and confidentiality of PLWH is paramount.[622] The protection of personal information in medical and scientific research is also a universally recognised right which not only relates to the right to privacy, but

---

619 R Amalia and Catherine Tucker, 'Privacy Protection, Personalized Medicine and Genetic Testing' (09 July 2015) https://www.ftc.gov/system/files/documents/public_comments/2015/09/00010-97509.pdf accessed 08 January 2022.

620 The Constitution of the Republic of South Africa, 1996. Section 14 provides that: Everyone has the right to privacy, which includes the right not to have
a. their person or home searched.
b. their property searched.
c. their possessions seized; or
d. the privacy of their communications infringed.

621 National Health Act 61 of 2003, section 14.

622 Margaret Bamford, *Work and Health: An Introduction to Occupational Health Care* (Springer Science + Business Media BV 1995) 55.

is also intertwined with the right to dignity[623] and how personal information is held and protected.[624]

4.7.1.1 NM v Smith (Freedom of Expression Institute as amicus curiae)

The case of *NM v Smith (Freedom of Expression Institute as Amicus Curiae)*[625] is a very relevant case, as it dealt specifically with the privacy of PLWH. In this case, the names and HIV status of applicants were disclosed and published in a biography without the individuals' consent. The respondents, in turn, argued that:

(i) the publication of the applicants' information was neither intentional nor negligent as the applicants' HIV status was not a private fact at the time the book was published. In fact, their names had previously been disclosed in an application to interdict the book's publication;
(ii) the publication was not unlawful in that the applicants had provided their consent to their names being used in the interdict application and at the various commissions of inquiry; alternatively
(iii) there was no malice on the part of the respondents in publishing the names and HIV status of the applicants. The High Court subsequently dismissed the action against the first and second respondents and ordered the third respondent to pay damages of R15, 000.00 to each of the applicants. It ordered that the applicants' names be deleted from the book, and that until such deletion had been made, no further copies of the book could be sold.

The applicants then (unsuccessfully) applied to both the High Court and the Supreme Court of Appeal for leave to appeal against that part of the High Court's judgment dismissing their action against the first and second respondents. The applicants then approached the Constitutional Court for the requisite leave to appeal.

Once before the Constitutional court, the applicants contended that the common law had to be developed to align with the protection afforded their rights to privacy, dignity and psychological integrity in terms of the Constitution of the Republic of South Africa, Act No. 108 of1996. The applicants also argued that those who negligently, and not

---

623 AC Steinmann, 'The Core Meaning of Human Dignity' (2017) 16(1) Potchefstroom Electronic Law Journal 1-32, 23. Maintains that "The concept of human dignity is relatively new in international and domestic constitutional law".

624 https://workplaceohs.com.au/legislation/record-keeping/medical-information-and-privacy accessed 17 June 2020.

625 *NM v Smith (Freedom of Expression Institute as Amicus Curiae)* 2007 (5) SA 250 (CC).

only intentionally, published unauthorised confidential medical information, should be held liable, unless if the public interest demanded otherwise.

The Constitutional Court held that (i) the publication by the respondents of the applicants' HIV status constituted wrongful publication of a private fact and that the applicants' right to privacy was breached by the respondents. The applicant's rights to dignity and psychological integrity were also violated by the respondents, in that details of their HIV status were published without their consent.

The Constitutional Court hence established that in view of the stigma attached to PLWH and the discrimination and prejudice following the disclosure of a person's HIV status warrants legal protection against gratuitous disclosure of such status. Madala J explains as follows:

> "The affirmation of secure privacy rights within our Constitution may encourage individuals to seek treatment and divulge information, encouraging disclosure of HIV which has previously been hindered by fear of ostracism and stigmatisation. The need for recognised autonomy and respect for private medical information may also result in the improvement of public health policies on HIV/AIDS."[626]

The Court in this instance expresses its sentiments in favour of individual rights and interests over and above those of science and the pursuit of knowledge, every possible care should be exercised in order to observe the privacy and the confidentiality of the patient.[627] To this extent, Madala J, in quoting from *Bernstein v Bester* (at paragraph 33), maintains that:

> *"*[A] very high level of protection is given to the individual's intimate personal sphere of life and the maintenance of its basic preconditions and there is a final untouchable sphere of human freedom that is beyond interference from any public authority. So much so that, in regard to this most intimate core of privacy, no justifiable limitation thereof can take place. But this most intimate core is narrowly construed. This inviolable core is left behind once an individual enters into relationships with persons outside this closest intimate sphere; the individual's activities then acquire a social dimension and the right of privacy in this context becomes subject to limitation."

Based on the expressions of Madala J, one may assume that participants who consent to participate in PGx may have concerns regarding how extensive the effects of their consent may be. For example, questions may arise as to the level of choice and control they have over their information being used, who has access to it, and what that means for them. People also expect an appropriate level of sensitivity to their data.

---

626 Constitution of the Republic of South Africa, Act 108 of 16

627 Timothy Caulfield and Nola Ries, 'Consent, privacy and confidentiality in longitudinal, population health research: The Canadian legal context' (2004) 12(1) 18-59 at 19.

The PLWH's rights to privacy are especially susceptible to compromise through genetic and genomic testing. Irrespective of this compromise, genetic and genomic profiling is imperative for the PGx practice.[628] The acceleration of "big data", together with rapidly developing technology, holds untapped potential for drug discovery and personalised healthcare platforms,[629] yet the risk of disclosure of sensitive personal information across different databases becomes increasingly evident, particularly in instances where personal information from one database is triangulated with information held in another database.

4.7.1.2 Protection of personal information in the National Health Act

Section 14 of the National Health Act[630] protects privacy through a provision titled "Confidentiality" as follows:

"(1) information concerning a user, including information relating to his or her

(2) Subject to Section 15, no person may disclose any information contemplated in health status, treatment or stay in a health establishment, is confidential, unless-

*(*a) the user consents to that disclosure in writing;
(b) a court order or any law requires that disclosure; or
(c) non-disclosure of the information represents a serious threat to public health."

Health professionals are expected to operate within the legal framework to protect the information of patients as also guided by the Health Professions Council of South Africa (HPCSA).[631] For purposes of personalised medicine an exception may be invoked based on Section 14(2) of the NHA to the effect that a patient consents in writing to allow for the genetic disclosure which forms part of medical treatment.[632]

The question arises as to what the requirements in the NHA regarding consent (which is the precursor to providing consent to disclose information) are. Section 6 provides the answer, which stipulates, under a heading titled "User to have full knowledge", that:

> "6. (1) Every health care provider must inform a user of -
> (a) the user's health status except in circumstances where there is substantial evidence that the disclosure of the user's health status would be contrary to the best interests of the user;
> (b) the range of diagnostic procedures and treatment options generally available to the user;

---

628 SB Haga and J Moaddeb, 'Comparison of delivery strategies for pharmacogenetic testing services' (2014) 24(3) Pharmacogenetics and genomics 347–350 at 139.

629 Biobanks and the Rise of Precision Medicine: Lessons from the Estonian Biobank Genome Webinar August 22, 2019 Sponsored by BC Platforms.

630 National Health Act 61 of 2003.

631 HPCSA, Confidentiality: Protecting and Providing Information (2008), para 4. Health Professions Council of South Africa is a statutory body, established in terms of the Health Professions Act.

632 National health Act 61 of 2003, section 14(2).

(c) the benefits, risks, costs and consequences generally associated with each option; and
(d) the user's right to refuse health services and explain the implications, risks, obligations of such refusal.
(2) The health care provider concerned must, where possible, inform the user as contemplated in subsection (1) in a language that the user understands and in a manner which takes into account the user's level of literacy".

The NHA furthermore provides for the protection of health records in Sections 16, 17 and 18, specifically with regard to access to health records; access to health records by health care providers, and also general provisions relating to the protection of health records.

These provisions in the NHA that protect a patient's personal information in the health care context is bolstered by the provisions of the Protection of Personal Information Act, discussed below.

4.7.1.3 Medicines and Related Substances Act

The South African Health Products Regulatory Authority (SAHPRA), governed by the Medicines and Related Substances Act, provides pharmacovigilance support to medicines' administration within its ambit. The objective of personalised medicine is to establish pre-medicine administration research on an individualised basis. Although SAHPRA guidelines are mostly directed towards an "after the event type of monitoring'' of ADRs, they provide no specific guidance on the monitoring of personal information as part of the development and manufacturing of personalised medicine.

Similar to other Regulatory Agencies around the world, the SAHPRA monitors the safety of health products to contribute to a better understanding of their possible adverse events when they are used outside the controlled conditions of clinical trials. Reports by consumers and healthcare professionals provide important information for SAHPRA's safety monitoring programme. SAHPRA in its PAIA manual (published in terms of Section 14 of the Promotion of Access to Information Act 2 of 2000) recognises the importance of patient information exchange and how the information needs to be handled with utmost protection. [633]

4.7.1.4 Other legislation protecting privacy and confidentiality

The precursors to POPIA[634] regarding access to patient information are Sections 32 of the Constitution (which protects the right to privacy), as well as Section 14 of the

633 SAHPRA, 'Promotion of Access to Information Act (PAIA) manual' https://www.sahpra.org.za/document/paia-manual/ accessed 20 November 2022.
634 Protection of Personal Information Act 4 2013.

(PAIA).[635] The two pieces of legislation provide for the right of access to information held by the State and to information held by another person that is required for the exercise and/or protection of any right. The exchange of information in respect of the facilitation of PGx is protected by POPIA which regulates not only the processing of personal information, but also the transfer and exchange of patient and research participant information. South African researchers share access to South African genomic data within SA, across Africa and with other international collaborators as an essential part of finding solutions to healthcare problems. The benefits of data sharing may include the optimal use of resources, increased statistical power, more reproducible science, promotion of new research on existing data sets and fostering of innovation, among others. These issues are interrogated in more detail in chapter 6 of this thesis.

In advancing personalised ART, genetics and genomics become a key focus. Legislation that protects the sharing and exchange of personal information will offer PLWH the opportunity to participate freely in trials involving PGx relating to ARVs.[636] The benefit of genomic profiling hinges on well-designed epidemiologic studies and clinical evaluations of recommended interventions, based on genotype.[637]

The WHO's monitoring system suggests a regular collection of data on HIV prevalence, treatment and the impact of adverse drug reactions in the South African population.[638] Viral load monitoring, timely fast-track diagnosis and treatment, as well as the notion of access to safe and efficient drugs in public health care and access to databases are of primary importance.[639]

There are many ways of describing the concept of treating a person based on genetic or other biomarker information.[640] A hallmark of this is the production of massive quantities of data, whose goals are that systems should integrate information from a variety of sources and to develop a comprehensive picture of relationships and

635 Promotion of Access to Information Act 2 of 2000.

636 Section 7(2) of the Constitution reads that the State should "respect, protect, promote and fulfil the rights in the Bill of Rights".

637 SB Haga and J Moaddeb, 'Comparison of delivery strategies for pharmacogenetic testing services' (2014) 24(3) Pharmacogenetics and genomics 347–350.

638 Guiding principles for ARV toxicity monitoring (WHO 2016 ARV guidelines) Workshop on management and reporting of adverse drug reactions related to ARVs,(Gaborone Botswana, 26 June 201), https://www.who.int/tdr/research/tb_hiv/ARV-Active-Toxcity-Monitoring-Gaberone-training-workshop-on-managment.pdf accessed 06 September 2019.

639 SB Haga SB and J Moaddeb, 'Comparison of delivery strategies for pharmacogenetic testing services' (2014) 24(3) Pharmacogenetics and genomics 347–350.

640 SG Haga SB and J Moaddeb, 'Comparison of delivery strategies for pharmacogenetic testing services' (2014) 24(3) Pharmacogenetics and genomics 347–350.

interactions between the components of biologic systems.[641] The legal regulation of so-called "Big Data" in the pursuit of PGx has indeed become a thorny issue for legislators trying to come to grips with the possible gaps that arise regarding the protection of personal information.

4.8 Lacunae in existing legal and policy framework regarding the regulation of PGx

The potential benefits and the role of PGx in the development of personalised ARVs are outlined in chapter 4 of this thesis. In essence these benefits may be described as maximising the efficacy and minimising the toxicity of ARVs, in particular to:

- improve the failure rate of current drug regimens;
- overcome the problems associated with kinetic variability of ARVs; and
- reduce the short- and long-term toxicities of the drugs.[642]

The year 2018 has been marked as a milestone year for genomic medicine as the South African Medical Research Council (SAMRC) has formed partnership with Beijing Genomics Institute (BGI), with the head office located in Cape Town."[643] The partnership gives effect to the importance of PGx to assist in the development of personalised medicines.[644] Saddled with the responsibility, the SAMRC needs to reassure the South African public that the collection of a variety of data types, including genetic and genomic data, is conducted in accordance with national policy and prescribed laws.[645]

Also in 2018, the Academy of Science of South Africa (ASSAf) emphasised the need "to develop policies, regulations and guidelines to address the ethical, legal and social implications (ELSI) of genetic and genomic work and that these need to be ethically and legally sound, culturally appropriate, feasible, enforceable and sustainable."[646]

---

641 Data curation services are needed to provide the infrastructure for data sharing. http://www.who.int/bulletin/volumes/94/4/16-172882/en/#R3 accessed 30 October 2019.

642 A Chawla, *et al*, 'A Review of Long-Term Toxicity of Antiretroviral Treatment Regimens and Implications for an Aging Population' (2018) 7(2) Infect Dis Ther 183–195.

643 SAMRC welcomes the collaboration as the facility is capable of conducting large-scale studies on whole genome sequencing in Africa. https://ehealthnews.co.za/genomics-centre-precision-medicine-sa/ accessed 23 September 2019.

644 PGx is used as one type of biomarker that is becoming widely used is an individual's genetic or genomic Information which facilitates an understanding of how affect an individual's response to treatment. https://www.eupati.eu/personalised-medicine/new-research-areas-personalised-medicines/ accessed 27 September 2019.

645 Academy of Science of South Africa, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications' (ASSAF 2018) http://dx.doi.org/10.17159/assaf.2018/0033 accessed 03 December 2021.

646 Academy of Science of South Africa, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications' (ASSAF 2018) http://dx.doi.org/10.17159/assaf.2018/0033 accessed 03 December 2021.

This 2018 Consensus Study by ASSAf on the legal, ethical, and social issues relating to human genetics and genomics in South Africa identified a number of gaps and limitations with regard to the current legal framework. The findings of this study are discussed below.[647]

It is submitted that legal *lacunae* regarding the implementation of PGx identified in this study can be traced to the following:

- limitations in the Constitution (Section 27(2) regarding the realisation of the right of access to health care services and its interpretation by the Constitutional Court[648] (discussed in Sub-section 4.5.1.2 of the current chapter);
- limitations in the statutory framework governing the development of personalised medicines (discussed in Section 4.8 of the current chapter 4);
- lack of appropriate training of health care practitioners and researchers in the new technologies, including PGx (discussed in Section 4.8.1 of the current chapter);
- lack of PGx studies and the absorption of the findings into the existing legal framework governing health research and personalised medicine development[649] (discussed in Section 4.10 in the current chapter).
- conflicting legal and ethical requirements relating to the collection, storing and sharing of genetic data and information (discussed in Section 6.4 of Chapter 6); and
- limitations in the statutory framework governing health research to address PGx and biobanking (discussed in Section 7.2 of Chapter 7 of this thesis);

The introduction of PGx in South Africa to date has predominantly focused on the assessment of TB drugs, limited to small settings, such as a few private laboratories or to pre-implantation genetic diagnosis.[650]

4.8.1 Genetic services

Key genetic services are available in South Africa for different health or private purposes (e.g., testing for genetic disorders, disability and birth defects; paternity testing) and in different settings, including services provided at tertiary care level, prenatal genetic diagnosis, diagnostic, predictive and carrier testing and genetic

---

647 Academy of Science of South Africa, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications' (ASSAF 2018) http://dx.doi.org/10.17159/assaf.2018/0033 accessed 03 December 2021.

648 *Soobramoney v Minister of Health*, KwaZulu Natal 1998 (1) 756 (CC).

649 https://ehealthnews.co.za/genomics-centre-precision-medicine-sa/ accessed 23 September 2019.

650 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423.

counselling services.[651] PGx should not be confused with genetic services. Although Chapter 3 of the NHA mandates the Director-General in Section 21(b)(vii) to make provision for genetic services ("The Director-General must issue and promote adherence to, norms and standards on health matters, including – genetic services"), no specific legislation governing genetics and genomics exists in South Africa. Gene editing and gene therapy also remain unregulated.

Consequently, lack of resources retards the training of personnel from carrying out genetic related tasks. The ASSAf Consensus Report states in Recommendation 14 as follows:

> "South Africa is currently in short supply of appropriately trained and skilled personnel at all levels of genetics and genomics work. To establish, build and maintain a service platform and large scale, sustainable genomics programmes for the benefit of a healthy nation, bearing in mind ethical, legal and social responsibility, will require technical, scientific, computational, bioinformatics and statistical analysis, as well as financial, legal and ethical expertise. More resources are therefore required to support genetic and genomic work, including training of genetics nurses, genetics counsellors, medical geneticists, medical scientists, bioinformaticists, biostatisticians and forensic scientists for the public and private sectors in South Africa". [652]

The ASSAf observation in 2018 follows exactly one decade after Kromberg, Sizer and Christianson[653] reported that in 2008, "the workload in most academic units remained heavy and qualified staff are overworked, as there were ten medical geneticists, ten genetic counsellors and 42 medical scientist/technologists to provide services to 49 million people." The effort to subject a patient to genetic testing is not onerous as appropriate test for a patient may require an analysis of only one base of DNA, or one gene, one panel, a whole exome or a whole genome.[654]

Despite South Africa's knowledge of PGx as an investigative tool that influences genetic and genomic variations on the individual's response to ARVs,[655] genetic services are under resourced and fragmented.[656] The debate regarding whether

---

651 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423.

652 ASSAf. Human genetics and genomics in South Africa: Ethical, legal and social implications. (2018) https://research.assaf.org.za/bitstream/handle/20.500.11911/106/2018_assaf_ethical_genetics_genomics_consensus.pdf?sequence=1&isAllowed=y (accessed 22 November 2022).

653 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423.

654 RC Green, *et al*, 'ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing' (2013) 15(7) Genet Med 565–574. 3

655 EJ Berm*, et al*, 'Economic Evaluations of Pharmacogenetic and Pharmacogenomic Screening Tests: A Systematic Review. Second Update of the Literature' (2016) 11(1) PLoS One.

656 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423.

Genetic services in South Africa should remain a function of the Department of National Health or co-ordinated by the department through the National Health Laboratory Service (NHLS), or whether the service should be delegated to the nine provincial Health Departments, continues to, and has over the past decade, been led to the slowing down of the development of these services.[657] This has severely impacted on the ability of persons to know and prevent potential disorders or diseases.[658]

Other factors impeding on access to genetic services include, among others, geographical barriers,[659] and financial barriers (particularly where a genetic counselling session and/or tests are too costly for the patient).[660] The lack of awareness, as well as ignorance of both health professionals and the public regarding the available genetic services and their value,[661] the cultural barriers, particularly related to fallacies and attitudes to genetic tests, are persistent.[662] These limitations are compounded by the difficulties in closing the disparities in health care in South Africa. Addressing and overcoming the disparities in health care between the rich and the poor remains a huge challenge for the South African government, especially in the context of the pandemic of HIV and AIDS, as well as the increasing prevalence of TB.[663]

---

657 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423.

658 D Meyersfeld, 'Genetics and its Role in Personalised Medicine' (2021) 2(2) South African General Practitioner 66-68.

659 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423, above where it is suggested that there is no genetic services are available in the rural areas, apart from the few outreach clinics provided by the academic centres.

660 See Kromberg "The narrowing of the disparities in health care between rich and poor is a formidable challenge for the new government, especially in the context of the pandemic of the human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS), as well as the increasing prevalence of tuberculosis (TB)."

661 G Wang and C Watts, 'The Role of Genetics in the Provision of Essential Public Health Services' (2007) 97(4) *Am J* Public Health 620–625.

662 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423.

663 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423.

Although the production of "block buster" generic drugs for HIV in the public arena is a boon to the South African government,[664] it does not involve PGx and ADRs remain a problem,[665] despite that huge costs are saved in this process.[666]

4.8.2 Policies

Despite the fact that South Africa has good policies in place to improve health care,[667] poor implementation and monitoring of policies, as well as poor management, have resulted in variable quality of care within the public health system.[668] Of further concern is that the 2016 *National HIV Testing Services: Policy* does not envisage the application of PGx.[669] Poverty and the AIDS epidemic are contributing factors to the mortality figures, and coupled with suboptimal implementation of the necessary interventions, result in unavoidable health system factors that contribute to unnecessary deaths.[670]

South Africa also has a plausible *Highly Active Antiretroviral Therapy* (HAART) rollout.[671] Health spending on HIV continues to be very stable in South Africa, both as a percentage of total government spending and as a share of the economy.[672] Notwithstanding, health expenditure varies between 3.7% and 3.9% of the gross domestic product (GDP).[673] This is due to the government benefiting from international hand-outs towards the HIV pandemic.[674]

4.8.3 Genetics and genomics training

Advancements in PGx have intensified the need for context-dependent, just-in-time genomics education for clinicians and other point-of-care workers. South Africa

---

664 Mylan expands access of ARV medicines to patients living with HIV/AIDS in South Africa. https://www.mylansa.co.za/en-za/news/2018/mylan-expands-access-of-arv-medicines accessed 27 September 2019.

665 DP Campion and FJ Dowell, 'Translating Pharmacogenetics and Pharmacogenomics to the Clinic: Progress in Human and Veterinary Medicine' (2019) 6(22) Front Vet Sci.

666 See Marteau at note 63 above at page 415.

667 H Coovadia*, et al, '*The Health and Health System of South Africa: Historical Roots of Current Public Health Challenges' (2009) 374(9692) Lancet 817-834.

668 E Kruk*, et al*, 'High-Quality Health Systems in the Sustainable Development Goals Era: Time for a Revolution Margaret' (2018) 6(11) The Lancet Global Health Commission 1196-1252.

669 https://www.tbhivinfosys.org.za/doc/hts-policy-28-july-final-copy_2016/ accessed 22 November 2022.

670 JG Kromberg, EB Sizer, and AL Christianson, 'Genetic Services and Testing in South Africa' (2013) 4(3) J Community Genet 413–423.

671 UNAIDS, 2010.

672 UNICEF, 'Health Budget South Africa' https://www.unicef.org/esa/sites/unicef.org.esa/files/2018-09/UNICEF-South-Africa-2017-Health-Budget-Brief.pdf accessed 08 January 2021.

673 UNICEF, 'Health Budget South Africa' https://www.unicef.org/esa/sites/unicef.org.esa/files/2018-09/UNICEF-South-Africa-2017-Health-Budget-Brief.pdf accessed 08 January 2021.

674 PEPFAR, CHAI and Bill and Belinda Gate's foundations have financed HIV/AIDS initiatives in South Africa. PEPFAR- USA Presidential Aid -Media Note Office of the Spokesperson Washington, DC 27 September 2018.

desperately requires an adequately genetics-trained health care professionals and researchers. Effective health care education, including genetics and genomics, will no doubt improve quality of care and patient health outcomes in general. Training for health professionals should include "a sound understanding of genetics terminology, inheritance patterns, diagnostics, family history assessment, screening, and how to make appropriate referrals".[675] Training should not only promote sensitivity regarding genetic information, appreciate psychosocial and cultural factors, but also be informed regarding relevant social, cultural, legal, and ethical concerns.

Online platforms, like the regional African Genomic Medicine Training Initiative (AGMT), an initiative established following a conference by the African Society of Human Genetics (AfSHG) and the Human Heredity and Health in Africa Consortium (H3Africa) in 2016, Senegal, may be helpful. The purpose of the AGMT is to respond to the needs for developing knowledge and skills in genomic medicine. Developments in genetics and genomics require swift, sensible, and responsible responses.[676] Recent developments, for example, include next-generation sequencing, genetic cohort studies and biobanks, which prompt ethical and legal questions relating to data management, quality of interpretation of data, data storage, data sharing, consent for re-use of data, as well as concerns about identifiability and privacy interests of sample donors.[677]

As rightly pointed out in the ASSAf Consensus Report, ethical, legal and social-related challenges should be prioritised for policymakers, researchers, clinicians and public health practitioners to maximise the benefits of genomic and genetic applications while minimising the risk of harm to people, which in turn, requires a dynamic education strategy.[678]

4.8.4 Regulation of genetic practitioners

As stated earlier in this thesis, SAHPRA is governed by the Medicines and Related Substances Act. The development and administration of medical devices have recently been inserted into the Medicines Act to fall within the ambit of SAHPRA's

675 ASSAf, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications (Department of Science and Technology, 2018) https://research.assaf.org.za/handle/20.500.11911/106 accessed 08 December 2022.

676 Pepper MS, Launch of the South African Human Genome Programme. South African Medical Journal. 2011;101(5):287-288.

677 ASSAf, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications (Department of Science and Technology, 2018) https://research.assaf.org.za/handle/20.500.11911/106 accessed 08 December 2022

678 ASSAf, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications (Department of Science and Technology, 2018) https://research.assaf.org.za/handle/20.500.11911/106 accessed 08 December 2022.

governance. The definition of medical devices in the Medicines Act (Section 1) includes diagnostic tests, and thus also cover genetic tests. It is expected that SAHPRA will be responsible for developing the regulatory framework for genetic tests and to establish guidelines for quality assurance in genetic laboratories.

Genetic practitioners in South Africa are health care practitioners and are required to be registered with the Health Professions Council of South Africa, as per the requirements of the Health Professions Act.[679] In the field of genetics, medical geneticists, also known as clinical geneticists, require specialisation in medical genetics through The Colleges of Medicine of South Africa and registration with the Medical and Dental (and Medical Science) Board of the HPCSA. The Medical Science Committee of the Medical and Dental Board registers medical scientists in the field of genetics and genetic counsellors. Technologists who practise in the field are required to register with the Medical Technology Board of the HPCSA.

Genetic practitioners that perform genetic testing for the purpose of diagnosis or to inform medical treatment should be registered with the HPCSA.[680] However, genetic practitioners who offer genetic tests with no direct clinical benefit and who don't have genetics training, are not regulated. The dilemma is that despite these practitioners being health professionals, it is not always clear when and to what extent they would require training in genetic methods and the interpretation of results to ensure that the feedback they provide to patients or clients is accurate, not misleading, and free of harm. It is imperative that the type of genetic tests that are used should be appropriate for the South African population and for the conditions being tested.

4.9 Genetic testing: patents and proprietary interests

Genetic testing, as well as PGx with the objective to develop personalised medicine, invokes notions of bio-capitalism[681] regarding human genes, fuelling intellectual property aspirations, which in turn, provokes a human rights agenda. The hope presented by personalised medicine in PGx means big business.[682]

---

679 Health Professions Act 56 of 1974.

680 Regulations defining the scope of the profession of medical science (2009), published under Government Notice R579 in Government Gazette 32244 of 22 May 2009.

681 M James, 'The Genealogy of a Gene. Patents, HIV/AIDS and Race' (2016) 22(2) The New Bioethics 155-157.

682 Jackson terms the emergence of 'biocapitalism' as the key obstacle to providing drug treatment and healthcare for all. The Genealogy of a Gene. Patents, HIV/AIDS and Race. By MYLES W. JACKSON. Pp. 336. Cambridge, MA: The MIT Press. 2015. (hb). ISBN 978-0-262-02866-0. See D Dickenson's in *Me Medicine vs We Medicine*: Reclaiming Biotechnology for the Common Good (2013), this practice has helped drive the market expansion of pharmaceutical and biotech Companies.

4.9.1 Association for Molecular Pathology v. Myriad Genetics, Inc 569 U.S. 576

The case of *Myriad*, heard by the US Supreme Court[683] premised on the challenge to the validity of gene patents in the United States, specifically regarding claims in patents owned by the respondent, Myriad Genetics which include isolated DNA methods and sequences to diagnose propensity to cancer, among others. Heard initially in the Southern District Court of New York, it was argued that the recognising the validity of these patents would promote investment in biotechnology and innovation in genetic research, whereas those opposed advanced the argument that recognising these patents would stifle innovation by preventing others from conducting cancer research; would restrict the options for cancer patients in seeking genetic testing, and finally, that these patents are not valid, as they relate to genetic information that is not inventive, but produced by nature. The District Court held that none of the challenged claims were patent eligible. Myriad hereafter appealed the decision to the US Court of Appeals for the Federal Circuit, which reversed and affirmed the district court's finding by holding that isolated DNA that does not exist alone in nature *can* be patented. However, the court held that although the drug screening claims were valid, Myriad's diagnostic claims were unpatentable.

Finally, when heard by the Supreme Court, the court held that merely isolating genes that are found in nature does not make them patentable. Intellectual property rights may potentially impede on the advancement of PGx and the development of diagnostic, therapeutic, and preventive strategies for improving the safety, effectiveness, and quality of health care in HIV.[684] Patents on genes that pertain to physical products of pharmaceutical programmes in the manufacture of ARVs have a negative impact on the pursuit of PGx.[685]

Patents are a lucrative endeavour for the gene researcher and may perversely deter a proper balance between drug development and PGx.[686] As discussed in chapter two of the thesis, IPRs in the form of patents tend to compromise the realisation of human rights. It is submitted that the rationality of the TRIPS Agreement[687] relating to the

683 *Association for Molecular Pathology v. Myriad Genetics, Inc* 569 U.S. 576.

684 FS Collins and VA McKusick, 'Implications of the Human Genome Project for Medical Science (2001) 285(1) JAMA 540-544.

685 T Pogge, *World Poverty and Human Rights* (2 edn Cambridge, UK: Polity Press 2008). The TRIPS Agreement became notorious as they suppressed LMICs generic competition in order to keep the prices of advanced ARVs much higher than the long run cost production.

686 Zakrison Tanya and Hamel Paul, 'Access to Medicines - The Global Debate Over "Free Trade" (2001) University of Toronto Medical Journal.

687 Paragraph 5 of the Doha Declaration on the TRIPS Agreement and Public Health.

manufacturing of medicines, and the mitigation thereof by the Doha Declaration, are undermined by the granting of patents in genes to medicine manufacturers.

It was mentioned in chapter three that many patents held by pharmaceutical companies with an origin in the USA and Europe, are based on research that didn't consider the varied genetic and genomic profiles of persons from Sub-Saharan Africa.[688] It is promising that a range of international instruments, committees and guideline documents refer to the need to observe and address ADRs, notably the United Nations Educational, Scientific and Cultural Organisation (UNESCO),[689] Council for International Organisations of Medical Sciences (CIOMS), Economic and Social Council (ECOSOC), European Society of Human Genetics (ESHG), the Human Genome Organisation (HUGO) and by extension, the HUGO Gene Nomenclature Committee (HGNC) and United Nations Convention on Biological Diversity.[690]

Recognition of the importance of PGx in promoting equity and fairness in the negotiation of mutually agreed terms between providers and users of genetic resources should be pursued.[691] Over the past decade, there has been a large shift in diagnostic options, moving from cell culture to rapid point-of-care testing.[692] Overall, the data obtained at the bedside should aid healthcare providers to improve and implement rapid relevant and personalised treatment.[693] It is important to reiterate that collaboration and innovation rather than IPR expropriation should drive down the price of live-saving drugs offered in a precision-based medication environment.[694]

4.10 Conclusion

The focus of this chapter, the existing regulatory framework governing the right to access to health care services, including PGx with the purpose of developing personalised HIV treatment (ARVs), against the backdrop of relevant international and regional instruments, reveals a fragmentary patchwork of provisions. Despite regional and global human rights obligations pointing to state responsibilities in prioritising access to health care and HIV treatment, the domestic regulatory framework regulates

688 ACS Akkari, *et al*, 'Pharmaceutical Innovation: Differences between Europe, USA and Pharmerging' Countries' (2016) 23(2) Gest. Prod. The Big Pharma refers to the pharmaceutical sector dominated by multinational companies from Europe and the USA.

689 Jeantine Lunshof and Guido de Wert, 'Pharmacogenomics, Drug Development, and Ethics: Some Points to Consider' (2004) 62(2) Drug Development Research 112-116.

690 ACS Akkari, *et al*, 'Pharmaceutical Innovation: Differences between Europe, USA and Pharmerging' Countries' (2016) 23(2) Gest. Prod.

691 Convention on Biological Diversity 'IX/12.Access and benefit-sharing' https://www.cbd.int/decision/cop/?id=11655 accessed 06 December 2022.

692 https://www.cbd.int/decision/cop/?id=11655 accessed 06 December 2022.

693 https://www.cbd.int/decision/cop/?id=11655 accessed 06 December 2022.

694 https://www.cbd.int/decision/cop/?id=11655 accessed 06 December 2022.

genetic research and services, as well as personalised medicine, to a very limited extent. Some of the gaps identified refers to lack of appropriate training by clinicians and researchers regarding genomic research; lack of coordinated professional regulation for genetic practitioners; policy and legislative gaps, fragmented regulation of data sharing and 'big data', to name but a few. The critical message to be taken from this discussion is that the full realisation of PGx in giving effect to the right of access to safe and effective ARVs can only be realised if implemented in a transparent and flexible regulatory framework, which, at present, does not exist.

The ensuing chapter is an exegetic reflection on the comparative legal perspectives regarding the monitoring of HIV and management of ADRs

Chapter 5

Comparative legal perspectives regarding the monitoring of HIV and management of ADRs

5.1 Introduction

The preceding chapter explored the legal framework governing the access of health care services in South Africa, including international and regional human rights obligations regarding individual's access of health care services and HIV treatment and personalised medicine. As outlined in the introduction to the previous chapter, Section 39(1) of the Constitution directs that:

> "[W]hen interpreting the Bill of Rights, a court, tribunal or forum - (a) must promote the values that underlie an open and democratic society based on human dignity, equality and freedom; (b) must consider international law; and (c) *may consider foreign law*"[695] (emphasis added).

This provision calls for a discussion on foreign law, where relevant, and *when* such discussion may assist in the interpretation of rights. For this reason, and on the strength of the motivation for the selection of the jurisdictions for legal comparison in Chapter 1 of this thesis, this chapter focuses on the key issues of comparison, namely, the monitoring of HIV and the management of ARVs in South Africa and the United Kingdom and Canada. The purpose of this comparison is not only limited to a search for best practices which may inform current laws and policies, but also on determining whether or not South Africa's advances in the management of HIV and ADRs has kept abreast of developments in this area, notably the development of personalised medicine in attempting to minimise or eliminate the effect of ADRs in HIV treatment.

There is a marked incongruity of divided loyalties between conflicting views about private health funding versus state-sponsored ART initiatives in each of these jurisdictions. Canada, as the sixth supporter of Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria,[696] acknowledges that South Africa is the most affected and infected country and therefore the fund focuses on the following priorities, namely:

- combating HIV/AIDS, tuberculosis and malaria;
- reducing child mortality;
- improving the rights and health of women and children; and
- promoting human rights in the context of HIV/AIDS, tuberculosis and malaria.

---

695 Section 3, Constitution of the Republic of South Africa Act No. 108 of 16

696 https://www.theglobalfund.org/en/ accessed 28 November 2022.

In November 2022, the United Kingdom, also identified as a longstanding partner and advocate of assisting the Global Fund, announced its commitment to increase its funding to GBP 1 billion for the following three-year period.[697]

The PGx has increasingly been recognised as a legislative and policy-directing issue.[698] Legislative and policy reforms follow evolving economic and public health contexts in different jurisdictions, which often dovetail developments in comparable legal systems. For example, the regulation of personal data protection in Europe (via the General Data Protection Regulation or GDPR)[699] was closely followed by the introduction of the Protection of Personal Information Act in South Africa.

5.2 Prevalence and monitoring of ADRs in HIV patients: comparisons between South Africa, Canada and the United Kingdom

5.2.1 South Africa

As alluded to in Chapter 4, the PGx in South Africa is steadily growing with research on the social, legal and ethical dynamics of genomics becoming the focus of study.[700] In 2016, a group of researchers from the University of Cape Town (the Pharmacogenomics and Drug Metabolism Research Group (PharmGx)), studied the genomic basis of human susceptibility to disease and differential response to therapeutic treatment (e.g., efficacy and toxicity). The group used genomic and molecular biology techniques to investigate genomic variation in drug metabolising enzyme genes[701] In 2018 African Pharmacogenomics Consortium (APC) was launched[702] with the view to pursuing the realities of sexually transmissible infections (STIs), communicable diseases, as well as the effects of the "clinical implementation for effective and safe use of medicine in the continent".[703]

---

697 https://www.theglobalfund.org/en/news/2022/2022-11-14-global-fund-applauds-uk-pledge-to-seventh-replenishment/ accessed 28 November 2022.

698 HIV continues to be a major global public health issue where in 2017 an estimated 36.9 million people were living with HIV (including 1.8 million children) – with a global HIV prevalence of 0.8% among adults, of concern is that around 25% of people around the world do not know that they have the virus. https://www.avert.org/global-hiv-and-aids-statistics accessed 13 September 2019.

699 https://gdpr.eu/ accessed 28 November 2022.

700 Assaf, PharmGx), APC and then Wits on Genomic variations in Africa.

701 A Matimba, M Dhoro and C Dandara, 'Is there a Role of Pharmacogenomics in Africa' (2016) 1(9) Global Health, Epidemiology and Genomics.

702 C Dandara, *et al,* 'African Pharmacogenomics Consortium: Consolidating Pharmacogenomics Knowledge, Capacity Development and Translation in Africa' (2019) 2(19) AAS Open Res.

703 C Dandara, *et al,* 'African Pharmacogenomics Consortium: Consolidating Pharmacogenomics Knowledge, Capacity Development and Translation in Africa' (2019) 2(19) AAS Open Res.

In 2017, the South African government released another national strategy titled: *National Strategic Plan on HIV, TB and STIs 2017-2022*,[704] addressing, among others, issues pertaining to HIV. The only significant difference between this strategy, the fourth of its kind, is its emphasis on "focus for impact", especially regarding the high-burden districts and key and vulnerable populations most heavily affected by HIV, TB and STIs. These areas and groups will require intensified focus to empower them, improve service access and reduce barriers to service uptake. The "focus for impact" approach is described as new and transformative strategy to achieve reductions in the mortality and morbidity associated with HIV and TB and morbidity from STIs.

Focus will turn more strongly on adolescent girls and young women; as well as key and vulnerable populations, including adolescent boys and young men. Regrettably, the strategy's focus and reference to HIV treatment did not include a consideration of PGx as an avenue to address ADRs associated with ARVs. The PLWH have specific needs that have been overlooked in the past and as a distinct group separate from other patients. However, their legitimate expectation of access to safe and effective ARVs continues to be delayed, including the implementation of PGx. However, the 2017-2022 strategy is a slight improvement on the earlier strategy. The 2012-2016 National Strategic Plan on HIV, STIs and Tuberculosis, prioritised an acceleration on antiretroviral drugs spending, even though health care in South Africa was hospi-centric,[705] which means that the public health system resorts to health problems being dealt with only at hospital level. [706]

South Africa's National Strategic Plan 2017-2022[707] identifies a number of groups that are particularly at risk of HIV transmission.[708] The HIV prevalence rate for teenagers and adults aged 15 to 49 was estimated to stand at 190%, whereas HIV prevalence among men who have sex with other men (MSM) stood at 26.8% in 2016.[709] Nationally, HIV prevalence among sex workers was estimated at 57.7%, with some variation between areas. The estimated prevalence for sex workers in

---

704 https://www.gov.za/sites/default/files/gcis_document/201705/nsp-hiv-tb-stia.pdf accessed 28 November 2022.

705 https://dictionary.cambridge.org/ accessed 30 October 2020.

706 The Lancet 'South Africa's AIDS response: the next 5 years' (2012) 379(1365) Lancet.

707 Signed by the then Deputy President Cyril Ramaphosa, "reflects the collective wisdom for achieving our vision of a South Africa free from the burden of HIV, TB and STIs Health information systems-From NSP 2017-2022.

708 South African National AIDS Council (SANAC) (2017) 'Let our actions count: National strategic Plan 2017-2022.

709 UNAIDS 'AIDSinfo' https://aidsinfo.unaids.org/ accessed 13 September 2019.

Johannesburg was the highest at an estimated 71.8%, followed by Durban with 53.5%, and finally, Cape Town with a prevalence rate estimated at 39.7%.[710]

Many of the initiatives in addressing HIV and AIDS in South Africa, as was discussed earlier in this thesis, were promoted by international developments, notably the WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS), which imposed global obligations on nations to participate in a quest to curb the pandemic through the development of national and international strategies towards the treatment of the disease.[711] The impact of UNAIDS 90-90-90 is also recognised in South Africa. The UNAIDS 90-90-90 plan of treatment assesses progress towards turning the HIV epidemic around. South Africa has made huge improvements in getting people to test for HIV in recent years and is now almost meeting the first of the 90-90-90 targets,[712] with 87% of South Africans being aware of their HIV status. South Africa also follows the 'test and treat' guidelines.[713] Accordingly, it is fair to conclude that the South African government, despite the initial governmental response to HIV (discussed in Chapter 2 of this thesis) and the fact that South Africa broke ground with the HAART roll out in October of 2003,[714] especially at a time when HIV was at its highest prevalence.[715] For this reason, it would be regrettable if the prospects of PGx in the development of personalised medicine in this context are ignored.

The South African Health Products Regulatory Authority (SAHPRA), as a Section 3A entity,[716] is an extension of the South African government. Moreover, SAHPRA ought to guide health professionals to use algorithms for reporting any negative factors or problems linked to product quality through the particular country's national system of reporting in order to alleviate consequences of medical negligence associated with ADRs.[717] PGx falls within the ambit of SAHPRA which is mandated to "oversee the

---

710 UNAIDS 'AIDSinfo' https://aidsinfo.unaids.org/ accessed 13 September 2019.

711 According to the UNDP and WHO, HIV has inflicted the "single greatest reversal in human development" in modern history (UNDP, 2005). Therefore, in response several countries have developed their own national strategies, for example, The South African National Strategic Plan (NSP) 2017 – 2022.

712 UNAIDS (2017) 'Ending AIDS: Progress towards 90-90-90 targets' (UNAIDS 20 July2017) https://www.unaids.org/en/resources/documents/2017/20170720_Global_AIDS_update_2017 accessed 13 September 2019.

713 South Africa is among the first countries in Africa to formally adopt Universal Test and Treat in accordance with the WHO new guidelines on HIV treatment. Health document: Re: Implementation of The Universal Test and Treat Strategy for HIV Positive Patients And Differentiated Care for Stable Patients.

714 N Nattrass, 'South Africa's "Rollout" of Highly Active Antiretroviral Therapy: A Critical Assessment' (2006) Centre for Social Science Research.

715 UNAIDS 'Aidsinfo' https://aidsinfo.unaids.org/ accessed 12 September 2019.

716 Public Finance Management Act 1 of 1999.

717 https://blog.talent360.co.za/general/south-african-health-products-regulatory-authority-sahpra/ accessed 26 November 2020.

regulation of health products which includes medicines, medical devices, in-vitro diagnostic tests and devices, radiation emitting products and devices used in health care and industry".[718] SAHPRA is tasked to oversee and regulate outcomes of ADRs by way of monitoring the enforcement of PGx compliance. Health care providers ought to use information from PGx testing to assist in medication and/or dosing decisions and ultimate prescriptions.[719]

In March 2020, SAHPRA issued the Guideline for Adverse Drug Reactions (ADRs) Reporting for Healthcare Professionals.[720] According to Regulation 40 of Medicines and Related Substances Act, as amended, a healthcare professional, veterinarian or any other person should inform SAHPRA, in the prescribed manner of any suspected ADRs or new or existing safety, quality or effectiveness concerns, occurring because of the use of any medicine or scheduled substance. In an attempt to prevent undesirable effects in patients due to sub-standard health products and inappropriate or unsafe use of health products, an ADR monitoring system was established in South Africa in 1987, coordinated by the Regulatory Pharmacovigilance unit of SAHPRA. This unit consists of the main office in Pretoria and a satellite office, National Adverse Event Drug Monitoring Centre (NADEMC), situated in Cape Town's Groote-Schuur Hospital and attached to the University of Cape Town's Clinical Pharmacology Division.[721]

Healthcare professionals are enjoined to report suspected ADRs even in the absence of all the facts or even if they are uncertain that the medicine is the cause of the reaction. Moreover, even if all the facts are not available at the time of reporting, the minimum information required for a valid case (i.e. information about the patient, suspected medicine, the reaction and information about the reporter) should always be included in the report.[722]

---

718 https://blog.talent360.co.za/general/south-african-health-products-regulatory-authority-sahpra/ accessed 26 November 2020.

719 Robeto Bin, Sarah Lorenzon and Nicola Lucchi, *Pharmacogenetics and Fundamental Rights* (Milan New York 2012).

720 SAHPRA, https://www.sahpra.org.za/wp-content/uploads/2020/04/ADR-Reporting-Guideline_HCPs_v1_for-commenting_March-2020.pdf accessed 29 November 2022.

721 SAHPRA, https://www.sahpra.org.za/wp-content/uploads/2020/04/ADR-Reporting-Guideline_HCPs_v1_for-commenting_March-2020.pdf accessed 29 November 2022.

722 SAHPRA, https://www.sahpra.org.za/wp-content/uploads/2020/04/ADR-Reporting-Guideline_HCPs_v1_for-commenting_March-2020.pdf accessed 29 November 2022.

It is regrettable that South Africa's ADRs are largely underreported, which appears to be a general concern in LMICs.[723] Underreporting of ADRs may be ascribed to the remote location of a number of ambulatory care clinics, primary healthcare (PHC) clinics and poor services in telecommunications; as well as inadequate training and low numbers of health care professionals.[724] In a specific study conducted by Haines et al, involving health care professionals in the public sector, nearly two-thirds of participants did not know how to report ADRs, where to report or when to report ADRs. Over half of the health care professionals indicated that the level of their clinical knowledge made it difficult to decide whether an ADR had occurred.[725]

5.2.2 United Kingdom

Unlike South Africa, the United Kingdom (UK) has a relatively small, concentrated HIV epidemic with an estimated number of 105,200 people living with HIV. Of this total, 94% are diagnosed and are aware that they have HIV; 98% of those diagnosed with HIV in the UK are on treatment, and 97% of those on treatment are virally suppressed.[726] Of concern are the findings which suggests that around 30% of the sexually active HIV-positive persons are men having sex with men (MSM).[727]

The Genomics Education Programme entered the UK medical arena in 2014.[728] The UK medical service, the NHS, acted positively and supported the transition to personalised medicine through the NHS Genomics Medicine Service, which intends to implement PGx in 2018. The objective of the NHS Genomic Medicine Service is to enable the NHS to harness the power of genomic technology and science to improve the health of our population and deliver on the commitments in the long-term plan of the NHS, whose objectives include the following:[729]

---

723 HM Haines, *et al,* 'Knowledge, Attitudes and Practices of Health Care Professionals Towards Adverse Drug Reaction Reporting in Public Sector Primary Health Care Facilities in a South African District' (2020) 76(1) European Journal of Clinical Pharmacology 991–1001.

724 HM Haines, *et al,* 'Knowledge, Attitudes and Practices of Health Care Professionals Towards Adverse Drug Reaction Reporting in Public Sector Primary Health Care Facilities in a South African District' (2020) 76(1) European Journal of Clinical Pharmacology 991–1001.

725 HM Haines, *et al,* 'Knowledge, Attitudes and Practices of Health Care Professionals Towards Adverse Drug Reaction Reporting in Public Sector Primary Health Care Facilities in a South African District' (2020) 76(1) European Journal of Clinical Pharmacology 991–1001.

726 HIV surveillance data in the UK by demographic characteristics and geographical region: Official statistics https://www.gov.uk/government/statistics/hiv-annual-data-tables accessed 28 November 2022.

727 EL Pufall, *et al*, 'Sexualized Drug Use (chemsex) and High-Risk Sexual Behaviours in HIV-Positive Men who have Sex with Men' (2018) 19(4) HIV Medicine 261-270. See also A González-Baez, *et al*, 'Sexualized Drug Use (Chemsex) is Associated with High-Risk Sexual Behaviors and Sexually Transmitted Infections in HIV-Positive Men Who Have Sex with Men: Data from the U-SEX GESIDA 9416 Study' (2018) 32(3) AIDS Patient Care STDS 112-118.

728 https://www.genomicseducation.hee.nhs.uk/about-us/ accessed 31 August 2022.

729 https://www.england.nhs.uk/genomics/ accessed 28 November 2022.

- being the first national health care system to offer whole genome sequencing as part of routine care, including for all children with cancer or children who are seriously ill with a likely genetic disorder;
- increasing access to molecular diagnostics and offer genomic testing routinely to all people with cancer;
- improving early detection and treatment of high-risk conditions including expanding genomic testing for familial hypocholesterolaemia;
- linking and correlating genomic data to help provide new treatments, diagnostic approaches and help patients make informed decisions about their care;
- delivering a single national genomic test directory covering use of all technologies from target genomic testing to whole genome sequencing;
- giving all patients an opportunity to participate in research for their individual benefit and to inform future care for other patients; and
- building a national genomic knowledge base to provide real world data to inform academic and industry research and development.

The UK follows a combination HIV prevention mode for handling HIV as suggested by UNAIDS.[730] According to UNAIDS, combination prevention are those programmes "that are rights-based, evidence-informed, and community-owned and that use a mix of biomedical, behavioural, and structural interventions, prioritised to meet the current HIV prevention needs of particular individuals and communities,"[731] in order to have the optimal sustained impact for minimising new infections.[732] Despite the strides made in the UK regarding the NHS Genomics Medicine Service, better alignment between the objectives of the latter and relevant HIV treatment programmes is required in order to better promote PGx in the context of HIV treatment specifically.

Current key components of combination HIV prevention in the UK include: condom provision, pre-exposure prophylaxis (PrEP), expanded HIV testing and prompt ART initiation following diagnosis.[733] Affordability of medicines is key to the management of

730 Introduced in 2003 as a strategy- Global HIV Prevention Working Group. 'Access to HIV Prevention: Closing the Gap, (2003) http://www.globalhivprevention.org/pdfs/Funding%20Report%20FINAL.pdf accessed 12 September 2019.

731 UNAIDS Discussion Paper (UNAIDS 06 October 2010) https://www.unaids.org/en/resources/documents/2010/20101006_JC2007_Combination_Prevention_paper accessed 14 October 2019.

732 O Barbara, *et al*, 'Combination Prevention: A Deeper Understanding of Effective HIV Prevention' (2010) 24(1) AIDS 70-80.

733 UNAIDS, 'Combination HIV Prevention: Tailoring and Coordinating Biomedical, Behavioural and Structural Strategies 10 to Reduce New HIV Infections' (UNAIDS 06 October 2010) https://www.unaids.org/en/resources/documents/2010/20101006_JC2007_Combination_Prevention_paper accessed 30 October 2019.

HIV through generic medicines offered by the National Health Service (NHS).[734] An HIV prevention approach helps ensure that individuals have access to the types of interventions that best suit their needs as their ART evolves.[735] The present English statutory right to health, set out in the Constitution of the National Health Service (NHS),[736] influences how the State is managing the HIV programme effectively. The UK is said to maintain a leadership role in science, and in this position, they need to elevate the standards as far as personalised medicine is concerned.[737]

Coleman and Pontefract discuss the causes of ADRs, the mitigating strategies as well as steps to be taken should such an event occur.[738] In the UK, detecting ADRs over the last fifty years was based on a spontaneous reporting system, known as the Yellow Card Scheme, operated by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM). The Yellow Card scheme traces its origin to the early 1960s, following the thalidomide disaster in the late 1950s. The scheme collects data on suspected ADRs related to all licensed and unlicensed medicines and vaccines, including those issued on prescription or purchased over the counter. A valid report requires four information items, namely: an identifiable patient, a reaction, a suspected medicinal product and an identifiable reporter. As much as possible information should be provided. It is noteworthy that around 25,000 ADR reports are filed per year, offering medicine regulators an insight into the occurrence of ADRs. Underreporting of ADRs is a huge concern. This limits the ability of systems to give accurate incidence data.

In 2014, NHS England and the MHRA issued a joint alert, titled “Improving medication error incident reporting and learning”, in terms of which ADRs occurring as a result of medication errors, reported to the National Reporting and Learning System (NRLS), will automatically be reported to the Yellow Card Scheme.[739]

---

734 https://www.nat.org.uk/about-hiv/hiv-statistics accessed 30 October 2020.

735 WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (December 2018) https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1 accessed 28 November 2022.

736 https://www.gov.uk/government/publications/the-nhs-constitution-for-england/the-nhs-constitution-for-england#patients-and-the-public-your-responsibilities accessed 28 November 2022.

737 The Lancet (Lancet Editorial, 06 January 2018) https://www.sciencedirect.com/journal/the-lancet/vol/391/issue/10115 accessed 06 December 2022.

738 JJ Coleman and SK Pontefract, ‘Adverse Drug Reactions’ (2016) 16(5) Clinical Medicine Journal 481-485.

739 JJ Coleman and SK Pontefract, ‘Adverse Drug Reactions’ (2016) 16(5) Clinical Medicine Journal 481-485.

5.2.3 Canada

Canadians living with HIV come from all facets of society and from all provinces.[740] Nearly half of these infections (48%) are among men having sex with other men. Other groups disproportionally affected by HIV in Canada include injection drug users (IDUs).[741] Unlike South Africa, the Public Health Agency of Canada defines provinces where HIV is endemic as those "where the prevalence of HIV among adults (age 15-49 years) is 1.0% or greater and one of the following: 50% or more of HIV cases are attributed to heterosexual transmission; a male to female ratio of 2:1 or less among prevalent infections; or HIV prevalence greater than or equal to 2% among women receiving prenatal care."[742]

Whilst the national diagnosis rate is estimated at 4.3 in 2020, the individual provincial and territorial HIV diagnosis rates are as indicated in Table 5.1 below:[743]

Table 5.1: Canada's provincial and territorial HIV diagnosis rates: 2020

Territories	2.3
British Columbia	2.6
Alberta	3.3
Saskatchewan	15.7
Manitoba	7.0
Ontario	3.5
Quebec	6.1 (previously diagnosed cases included)
Atlantic	1.3

Extrapolated from Table 5.1 above is that Saskatchewan exceeds the Canadian national average of HIV cases per capita, but there was an escalation in 2021, with the provincial rate roughly three times the national average.[744] The reason for this increase may be ascribed to the increase in intravenous drug use. Already in 2016, a group of doctors in Saskatchewan urged the provincial government to declare a state of emergency on public health in regard to HIV and AIDS in the province at a time

740 Q Yang, *et al*, 'Estimates of the Number of Prevalent and Incident Human Immunodeficiency Virus (HIV) Infections in Canada, 2008' (2010) 101(1) Canadian Journal of Public Health 486–490.

741 RS Remis, 'HIV Incidence Among Injection Drug Users in Vancouver' (2002) 166(7) JAMC 908.

742 Government of Canada, 'Summary: Estimates of HIV Incidence, Prevalence and Proportion Undiagnosed in Canada, (2014) https://www.canada.ca/en/public-health/services/publications/diseases-conditions/summary-estimates-hiv-incidence-prevalence-proportion-undiagnosed-canada-2014.html accessed 22 November 2022.

743 Government of Canada, 'HIV in Canada: 2020 Surveillance Highlights' https://www.canada.ca/en/public-health/services/publications/diseases-conditions/hiv-2020-surveillance-highlights.html accessed 29 November 2022.

744 L Stein, 'Record number of HIV cases reported in Saskatchewan' (CJME, 1 June 2022) https://www.cjme.com/2022/06/01/record-number-of-hiv-cases-reported-in-saskatchewan-not-done/ accessed 28 November 2022.

when the rate of infection was twice the national infection rate.[745] Since then, the infection rate has increased to three times the national average.

Regarding Canada's progress with the 90-90-90 targets for HIV in 2020, reports show that an estimated 62,790 Canadians were living with HIV at the end of 2020. In addition, 90% of PLWH were diagnosed; 87% of people diagnosed with HIV were on treatment and 95% of people on HIV treatment had a suppressed viral load.[746]

The turnaround in the diagnosis rate of British Columbia merits mention. In 1992, British Columbia had the worst HIV epidemic in Canada, with two new HIV diagnoses and one person dying of AIDS every day. In response to the dilemma, a British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) was initiated in Vancouver, British Columbia. In 2020, British Columbia started to experience an annual decline in the rate of new HIV diagnoses. The decrease is currently under 250, which is the second lowest rate in Canada and is partly attributed to the greater expansion of HAART coverage in this province.[747] The BC-CfE was the first centre worldwide to pioneer province-wide testing and roll-out of antiretroviral drugs (ARVs) using the treatment-as-prevention strategy.[748] The latter strategy proved that it was possible to nearly eliminate HIV transmission with this approach, which is the inspiration behind the UN 90-90-90 target to diagnose 90% of people with HIV, ensure at least 90% receive ARVs, and that at least 90% of those treated are virally suppressed by 2020.

One of the foundational programmes of the BC-CfE, the Drug Treatment Programme (DTP), is funded by the provincial government (PharmaCare) to distribute anti-HIV drugs based on guidelines generated by the Therapeutic Guidelines Committee.[749] Information from all participants is entered into a database, providing data for clinical and virologic outcome studies of patients receiving ART. This database acts as a registry of HIV-treating physicians in the province, as well as an "early warning system"

---

745 https://www.cdnaids.ca/hiv-in-saskatchewan/ accessed 28 November 2022.

746 Government of Canada, 'Canada's Progress Towards Global HIV Targets (90-90-90)' (2020) https://www.canada.ca/en/public-health/services/publications/diseases-conditions/canada-progress-towards-global-hiv-targets-90-90-90-2020.html accessed 28 November 2022.

747 British Columbia Centre for Excellence in HIV and AIDS https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)01100-9/fulltext accessed 29 November 2022.

748 British Columbia Centre for Excellence in HIV and AIDS https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)01100-9/fulltext accessed 29 November 2022.

748 British Columbia Centre for Excellence in HIV and AIDS https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)01100-9/fulltext accessed 29 November 2022.

749 British Columbia Centre for Excellence in HIV and AIDS https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)01100-9/fulltext accessed 29 November 2022.

to alert government about the trajectory of the disease. The Drug Treatment Programme (DTP) ensures that all at-risk medically eligible persons living with HIV in British Columbia have access to cost-free antiretroviral therapy.

In Canada, adverse drug reactions are regulated in terms of post approval surveillance of health products, governed by the Food and Drugs Act[750] and Regulations.[751] The voluntary reporting of adverse reactions by health professionals and consumers is the primary way for the monitoring of the safety and effectiveness of marketed health products to obtain information regarding ADRs. These individual reports are the only information source concerning ADRs that were previously undetected, or changes in product safety and effectiveness profiles to marketed health products.[752] The coordination of national adverse reaction reporting activities is the responsibility of the Marketed Health Products Directorate of Health Canada. In this regard, reports are collected by seven Regional AR Centres (i.e., British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Québec and Atlantic), as well as by the National Office, which is located in Ottawa, Ontario.[753] An initial review of the completeness and quality of reports is done by the Regional Centres, after which the reports are then processed and further analysed at the National Office.

Information regarding the safety and efficacy of medicines is also obtained through active surveillance activities which include the regular periodic collection of case reports from health professionals and health facilities; publications in scientific journals; or risk-communications from regulatory agencies in other countries.[754] However, the reporting mechanism raises issues of inefficiency and maladministration with specific reference to ADRs.[755] The guidance documents are administrative instruments that do not have the effect of force of law, and therefore, allow for flexibility

750 Food and Drugs Act (R.S.C., 1985, c. F-27).
751 Food and Drug Regulations (C.R.C., c. 870).
752 Government of Canada, 'Adverse Reaction Information' https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-information.html accessed 29 November 2022.
753 Government of Canada, 'Adverse Reaction Information' https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-information.html accessed 29 November 2022.
754 Government of Canada, 'Adverse Reaction Information' https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-information.html accessed 29 November 2022.
755 NS Rawson, 'Canada's Adverse Drug Reaction Reporting System: A Failing Grade' (2015) 22(2) J Popul Ther Clin Pharmacol 167-172.

in approach. As such, this paucity in legal effect is not always regarded in a positive light.[756]

5.3 Conclusion

There are marked differences in the HIV prevalence portrayed in the statistics per jurisdictional administration, with South Africa occupying an unenviable top position. All the jurisdictions discussed have their own HIV prevention and treatment programmes. The United Kingdom and Canada are leading in reaching and maintaining the WHO's 90-90-90 targets, with South Africa lagging behind. It has to be mentioned that before any HIV intervention programmes were implemented, South Africa's baseline was completely different from those in the other two jurisdictions.

The management of ADRs also varies from one country to another. All three jurisdictions have legal or administrative mechanisms for the management of ADRs, located in the context of the medicine regulatory framework. The ADR's spontaneous reporting, which is currently the basic method for collecting information about adverse post-marketing risks and events, is followed in all three jurisdictions. Regrettably, South Africa's ADRs are highly underreported, compared to those in the UK and Canada.

Both the UK and South Africa demonstrate some laxity regarding the benefits of PGx and have only recently started to explore the applications of PGx research in addressing ADRs. South Africa's wide and divergent genetic diversity points to greater gene variation, which renders genetic sequencing for the purpose of developing personalised medicines less economically viable. The same argument could apply to Canada, but to a lesser extent in the UK - especially considering that these two countries are high-income countries, and not a low-income country such as South Africa.[757]

The PLWH need to be made aware of the advantages of PGx testing in order to enable their reporting of ADRs and appreciate the information leaflets found in their ART medication. In South Africa, public patients are likely to find their medication packaged in non-original containers. Therefore, information to predict the likelihood of medication response and/ or risk for adverse drug reactions based on PGx could be missed. Healthcare providers may use information from pharmacogenomics testing to assist in

---

[756] NS Rawson, 'Canada's Adverse Drug Reaction Reporting System: A Failing Grade' (2015) 22(2) J Popul Ther Clin Pharmacol 167-172.

[757] F Albalwy, *et al*, 'A Blockchain-Based Framework to Support Pharmacogenetic Data Sharing, (2022) 22(1) Pharmacogenomics Journal 264-275.

medication and/ or dosing decisions. Some examples include choosing a drug that may have better efficacy, avoiding drugs with a high-risk of toxicity or adverse drug reaction, such as hypersensitivity, or adjusting the dose of a drug or determining when closer monitoring is needed.[758]

The next chapter presents discussions premising on data protection and data sharing issues arising from PGx: comparisons between South Africa, the United Kingdom and Canada.

[758] Association for Molecular Pathology Position Statement: Best Practices for Clinical Pharmacogenomic Testing – 04 September 2019.

Chapter 6

Data protection and data sharing issues arising from PGx: comparisons between South Africa, the United Kingdom and Canada

> "Data sharing is increasingly regarded as an ethical and scientific imperative that advances knowledge and thereby respects the contributions of the participants".[759]

6.1 Introduction

The ethical, scientific and the legal imperatives on data sharing are intended to serve private as well as public subjects who are participants in research studies. To this end, governments and Big Data creators. Big Data is a term denoting "the three Vs" – volume (which is vast amounts of data), variety and velocity of data which a data scientist or user can access and analyse.[760] Such data need to be sensitised to the ethical and legal responsibilities regarding data sharing in the context of PGx and the development of personalised medicines.[761] The fulfilment of scientific research in PGx can only take place through the resolution of problems associated with ADRs within the ethical principles of advocacy in patient's health information management.[762]

The PGx requires existing and stored data for purposes of matching genes with the required type of compatible medication to the patient's health care needs.[763] To this end, registers need to be accessible to describe tests and provide more robust search methods[764] to facilitate the outcome of personalised medicine. As mentioned earlier in this thesis, genetic and genomic research collaboration relies on the sharing of health data between researchers.

With the advent of PGx, privacy of an individual or a group associated with the affected person is compromised because PGx utilises genetic profiles[765] and requires the analysis of an individual's genetic information for comparison of such information to a larger community's profile. Reactions to specific ARVS will influence the determination of an alternative drug that may yield effective results to treat a given health condition to an individual or group of people.[766] However, there is an anticipated incongruity in

---

759 BM Knoppers, *et al*, 'Towards a data sharing Code of Conduct for international genomic research (2011) 3(46) Genome Medicine.

760 G Cohen, *et al*, *Big Data, Health Law, and Bioethics* (Cambridge University Press 2018).

761 G Cohen, *et al*, *Big Data, Health Law, and Bioethics* (Cambridge University Press 2018) 7.

762 S Helbig and LB Harman, *Ethical Challenges in the Management of Health Information* (2 edn Jones Bartlett Publishers Canada 2006) 611.

763 https://genetictestingseminars.education/pgx-pharmacogenetic-test accessed 25 April 2020.

764 WS Rubinstein, *et al*, 'The NIH Genetic Testing Registry: A New, Centralized Database of Genetic Tests to Enable Access to Comprehensive Information and Improve Transparency' (2013) 41(1) Nucleic Acids Research 925-935.

765 BR Goldman, 'Pharmacogenomics: Privacy in the Era of Personalized Medicine' (2005) 4(1) North-western Journal of Technology and Intellectual Property.

766 G Cohen, *et al*, *Big Data, Health Law, and Bioethics* (Cambridge University Press 2018) 57.

divided loyalties and conflicting views about PGx and data sharing, especially in cases where the potential to claim IPR is foreseen.[767]

6.2 Collection of patient data for purposes of PGx

Collecting patient data to provide direct healthcare services (commonly called "primary use") is the cornerstone for healthcare practice, which in some cases requires the prescription of medicine.[768] A dedicated part of pharmacology[769] in relation to HIV, developed and emerged as a reactionary pressure in the face of the HIV pandemic.

The creation of "Big Data" creates opportunities for accessing recorded data relating to ADRs.[770] Therefore, clinical trials in ARVs rely on Big Data, as well as on real-world evidence of the disease, electronic clinical data based on the number of diagnosis and tests, mobile device-driven data; as well as action groups and communities.[771] Electronic health and medical records are some of the new data sources that are available to investigate adverse drug reactions.[772]

Researchers and health care personnel often resort to electronic health record systems to access the medical history of patients to facilitate the sharing of patient information between multiple facilities and agencies.[773] In 1991, the Institute of Medicine (IOM)[774] issued a report titled: *The Computer-Based Patient Record* (CPRs), which proposed the elimination of paper-based records within a period of 10 years.[775] With medical records becoming available electronically, despite possible extended uses and accessibility, the risks of inadvertent disclosure or personal information - not to mention threats relating to cybersecurity and hacking - are becoming more

---

767 The Sunday Morning Herald, 7 October 2015. The High Court ruling against patenting BRCA1 means Myriad Genetics no longer own the mutation test and scientists outside the company will be able to extend research into the breast cancer gene, explains health editor Amy Corderoy.

768 MN Sarkies, *et al*, 'Data Collection Methods in Health Services Research: Hospital Length of Stay and Discharge Destination' (2015) 6(1) Applied clinical informatics 96-109.

769 Webster's Dictionary defines pharmacology as 1: the science of drugs including their origin, composition, pharmacokinetics, therapeutic use, and toxicology. 2: the properties and reactions of drugs especially with relation to their therapeutic value.

770 G Cohen, *et al*, *Big Data, Health Law, and Bioethics* (Cambridge University Press 2018) 79.

771 Civil Society Organisations as well as Treatment Action Campaign Group, for example, Friend of Section 27 in South Africa.

772 Richard Young, 'Impact of Data Management on Clinical Trials: New Study**'** (Pharmaphorum 18 December 2017) https://pharmaphorum.com/r-d/views-analysis-r-d/impact-data-management-clinical-trials-new-study/ 10 October 2019.

773 Technology Advice for Small Businesses**, '**EHRs vs paper records: Which is better?' (TechAdvisory 04 February 2019) https://www.techadvisory.org/2019/02/ehrs-vs-paper-records-which-is-better/ accessed 12 October 2019.

774 The Institute of Medicine was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public.

775 DE Detmer and EB Steen 'The Computer-Based Becord: Patient Moving from Concept Toward Reality' (1996) 42(1) Int J Biomed Comput 9-19.

prevalent. Some of the pertinent questions regarding the protection of personal health information of PLWH in the context of PGx, relate to the issue of the legal regulation of biobanks; consent to the secondary sharing of data; return of incidental findings; consent to the further utilisation of biological samples (for purposes other than those stated in the original consent); and individual and family privacy.[776] For purposes of providing high-quality care in the interests of PLWH, drug manufacturers and clinicians should have access to testing options on the patient's DNA to facilitate PGx.[777] The creation of DNA databases inevitably involves a balancing act between the promotion of science on the one hand; as well as protecting the interests and right of the research participants, on the other.[778]

In 2018, questions related to DNA bio-banking were debated during an international workshop organised by the European Society of Human Genetics Public and Professional Policy Committee in Paris, France. [779] The importance of banking of genetic material was repeatedly emphasised at this workshop. Bio-banking is a complex endeavour, which requires facilities, researchers and acceptance by participants. Furthermore, bio-banking enables the Constitution of large collections, sharing of samples, multiple testing on the same samples, and repeating testing over the years.[780] Already in 2002, the international standardisation of ethical requirements and policies in collaboration with the International Ethics Committee of the Human Genome Organisation (HUGO) stated that human genomic databases should be considered global public goods.[781] Therefore, the protection of personal information should not be violated.[782]

---

776 Edward Dove and Mark Phillips, 'Privacy Law, Data Sharing Policies, and Medical Data: A Comparative Perspective' (2015) 4(1) Springer International Publishing 639-678.

777 LV Kalman, et al, 'Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting' 2016 99(2) Clin Pharmacol Ther 172-185.

778 'The Under 30 Using Genomic Data To Find Cures And Save Billions' (Forbes 15 Feb 2017) https://www.forbes.com/video/5254637751001/using-genomic-data-to-find-cures-and-save-billions/?sh=39bdb52f1750 accessed 15 september 2019.

779 HC Howard, *et al,* 'Public and Professional Policy Committee of the European Society of Human Genetics' (2018) 26(1) Eur J Hum Genet 1-11. One small edit for humans, one giant edit for humankind? Points and questions to consider for a responsible way forward for gene editing in humans.

780 Jakub Pawlikowski, Jaroslaw Sak and Krzysztof Marczewski, 'The Analysis of the Ethical Organizational and Legal Aspects of Polish Biobanks Activity' (2010) 20(6) European Journal of Public Health 707–710.

781 GP Brownman 'Human Genome Organisation (HUGO), Ethics Committee: Statement on human genomic databases, December 2002' (2003) 14(1) J Int Bioethique 207-210.

782 The Constitution of the Republic of South Africa, 1996 at Section 8(3) provides that: there are possibilities of obtaining ordinary legal relief when there has been a violation. Therefore, the mind of legislature on the protection of personal information should be respected.

This chapter specifically addresses the protection of personal information in the context of PGx by comparing the legal frameworks governing data protection in South Africa, Canada and the United Kingdom. The justification for a legal comparison involving the UK and Canada has been stated earlier. The South African legal system shows legal influences from English law - both in the common and statutory law -[783] whilst the Canadian Constitution has played a role in the development of Constitutional jurisprudence in South Africa.[784] South African laws and principles regarding biotechnological genesis of PGx and data sharing appears to be delicately poised between the Canadian and the UK experiences.

The Canadian laws are influenced by Constitutional jurisprudence, while English law is allied to common law, except where extensive public health laws exist on an aspect at hand that is contrary to the tenets of the Constitution of South Africa. Historically, South Africa was more influenced by English law and is currently following a democratic dispensation which is reliant on Section 39 of the Constitution of the Republic of South Africa, 1996. The Bill of Rights does not deny the existence of any other rights or freedoms that are recognised or conferred by common law, customary law or legislation, to the extent that they are consistent with the Bill.

Constitutional influences and common law as applied in court decisions have a bearing on the protection of personal information, as the biotechnology of PGx is heavily reliant on the study and the sequencing of genes.[785] For this reason, the comparative analysis of relevant provisions across the three jurisdictions may expose some of lacunae or best practices regarding the protection of personal information. There are now mandatory investigation and fines, data breach notification, and significantly increased enforcement[786] as a result of the liabilities created by HITECH modifications to HIPAA several years ago in the United States. Such enforcement extends to the General Data Protection Regulation (GDPR) in the European Union and updates to the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada as well as changes across the globe to other regulations. An examination of the *lacunae* in legal

783 Barrat, A and Snyman, P. Globalex: Researching South African Law (2018). https://www.nyulawglobal.org/globalex/South_Africa1.html#ahistorical (accessed 29 November 2022). *Carmichele v Minister of Safety and Security* 2001 (4) SA 938 (CC). The court maintained that South Africa is obligated to develop the common law, which suggests that the development of the common law is not discretionary.

784 The Canadian Charter, South Africa and the Paths of Constitutional Influence. R Albert and D Cameron, *Canada in the World: Comparative Perspectives on the Canadian Constitution* (Cambridge: Cambridge University Press 2018) 371-396.

785 G Potamias, *et al,* 'Deciphering next-generation pharmacogenomics: an information technology Perspective' (2014) 4(7) Royal Society 2046-2441.

786 https://naidonline.org/programs/doctors-office-marketing/ accessed 20 April 2020.

(legislation and case law) provisions as they impact on data sharing and the protection of personal information, is highlighted as well in this chapter. 'Big Pharma''s platforms,[787] artificial intelligence (AI) and "Pandomics" are terms that have recently received attention in this regard.[788]

6.3 Confidentiality in medical records and personal information

For the people living with HIV, laws that protect the private life of an individual, family and the community in genomic research should generally take into consideration the privacy issues relating to access and sharing of health and medical data.[789] In a clinical context, a patient's electronically stored medical or health record may contain full and further ancillary information, which may refer to personal details unconnected with clinical data. A research participant's personal information, on the other hand, should be protected from unwarranted and unlawful disclosure or intrusion at all times.

Normally, a research ethics review committee would oversee research conducted with human participants in accordance with the provisions of the NHA and relevant regulations, including the 2015 Department of Health Guidelines on Ethics in Health Research.[790] Personal information is often de-identified or anonymised in respect of the Guidelines on Ethics in Health Research. In addition, the provisions of the Protection of Personal Information Act apply to the protection of personal information in both the clinical and research contexts. Although patient information should remain privileged and protected, Section 15(1) of the NHA allows for the disclosure of a patient's health care information "for any legitimate purpose".[791] As stated in Chapter 4 of this thesis in relation to the protection of privacy, medical records should be secured in a safe place where only authorised users can have access. Moreover, Section 16 of NHA promotes access[792] to health care records by health care provider, provided the information is shared with the authorisation of the patient.

---

787 Robert Blaskiewicz, 'The Big Pharma Conspiracy Theory' (2013) 22(4) Good Phama 1-3.

788 The power of exploring shared electronic data using visualization to enable exchange of all relevant information between the Big Pharma from different countries. https://pandomics.com/access accessed 16 April 2020.

789 MM Mello and LE Wolf (2010). 'The Havasupai Indian Tribe Case-Lessons for Research Involving Stored Biologic Samples' (2010) 363(3) The New England journal of medicine 204–207.

790 https://www.health.gov.za/nhrec-guidelines/ accessed 29 November 2022.

791 The National Health Act 61 of 2003 refers to Access to health records at Section 15, as:
(1) A health worker or any health care provider that has access to the health records of a user may disclose such personal information to any other person, health care provider or health establishment as is necessary for any legitimate purpose within the ordinary course and scope of his or her duties where such access or disclosure is in the interests of the user.
(2) For the purpose of this section, personal information as defined in section 1 of the Promotion of Access to Information Act, 2000 (Act No. 2 of 2000).

792 National Health Act 61 of 2003, Section 16 provides that: A health care provider may examine a user's health records for the purposes of-(a) treatment with the authorisation of the user;

It is widely recognised that genetic information is a particularly sensitive form of personal information, [793] which is also recognised in POPIA, which categorises genetic information as "special personal information" in Section 32(5). This definition, coupled with the fact that Section 32(1)(b)(ii) of the POPIA allows insurance companies to process such special personal information as part of their "performance of an insurance or medical scheme agreement". Such sensitivity leads to further concerns, as health insurance companies can create subsidiary companies that use genetic information for commercial purposes or lead to the establishment of intellectual property rights in genomic data sets.

Genetic samples normally comprise blood samples or cheek (buccal) swabs, which are regulated as "human biological material" by the Regulations Relating to the Use of Human Biological Material.[794] Although South African law does not regulate ownership in genetic information, it is general practice that genetic samples or "banked" DNA is owned by the depositor until it is stipulated otherwise that the biobank owns such DNA collection, and that the extracted information is owned by the researcher or team responsible for creating it.[795]

Regardless of the literary quality and its expression mode, the definition of a "literary work" in the South African Copyright Act includes tables and compilations of data kept or embodied in a computer or a medium used in conjunction with a computer.[796] Hence, a curated data set that contains genetic information may qualify as a literary work in which the creator of such a data set enjoys exclusive copyright that will enable him or her to reproduce the data set in any form or manner, publishing the set of data and causing it to be transmitted in a diffusion service, which effectively renders it commercialised.[797] To make matters worse, the data set's creator enjoys the IPR to the exclusion of the subject of the data (or patient and research participant).[798]

(b) study, teaching or research with the authorisation of the user, head of the health establishment concerned and the relevant health research ethics committee.
(2) If the study, teaching or research contemplated in subsection (1)(h) reflects or obtains no Information. as to the identity of the user concerned, it is not necessary to obtain the authorisations contemplated in that subsection.

793 Leone Skene, 'Legal regulation of genetic testing: balancing privacy and family interests' Legal Perspectives in Bioethics 208-218.

794 Regulations Relating to the Use of Human Biological Material, issued in terms of the NHA in GN R177 in GG 35099 of 2 March 2012.

795 M Botes, A Olckers and M Labuschaigne, 'Data Commercialisation in the South African Health Care Context' (2021) 24 PER / PELJ 1-35.

796 Definitions, Section 1 –"Literary Works"(g), Copyright Act 98 of 1978 as amended by s 50(e) of the Intellectual Property Laws Amendment Act 38 of 1997.

797 Section 6 of the Copyright Act 98 of 1978.

798 M Botes, A Olckers and M Labuschaigne, 'Data Commercialisation in the South African Health Care Context' (2021) 24 PER / PELJ 1-35.

Pharmacogenomic research relies on utilisation of clinical genetic testing, research testing, as well as diagnostic testing to reveal and disclose both the individual's genetic structure and the lineage genetic structure. The main differences between clinical genetic testing and research testing can be explained with reference to the purpose of the test and the recipient of the results. For the PLHW, the tests will seek to diagnose for HIV as well as test for the genetic stage of the virus.[799] The goals of research testing include finding unknown genes, learning how genes work, developing tests for future clinical use, and advancing the understanding of genetic conditions as well as the facilitation of the success of PGx.[800]

6.4 Data sharing of stored personal information

One of the major themes characterising the genome era has been the promotion of a policy of open data-sharing, which calls for protecting personal information. In recent years, sharing of electronic patient data for public health use has been given increased attention.[801] The principle of data sharing has advanced as a backbone of research which buttresses the notion of the availability of tons of data on patients' health, medication use, and imaging results, where software developers can use the information to develop and refine models to spot patterns that can be applied to improve healthcare.[802]

Data sharing is an internationally acclaimed endeavour, and is accordingly more about different types of disclosures, often involving many organisations and very complex information chains. These chains grow ever longer, criss-crossing organisational platforms to the extent of national boundaries.[803] During 2008 and 2009, a focus group of 10 members convened in Durham, North Carolina to explore attitudes about how genomic research data is shared amongst the research community, communication of these practices to participants and how different policies may influence participants'

799 https://emea.illumina.com/science/technology/next-generation-sequencing.html accessed 15 September 2020.

800 https://www.mayoclinic.org/tests-procedures/genetic-testing/about/pac-20384827 accessed 28 March 2021.

801 E Bell, *et al*, 'Patient Perspectives About Decisions to Share Medical Data and Biospecimens for Research' (2019) 2(8) Journal of the American Medical Association.

802 Future Agenda.

803 H Carmen, *et al*, 'Barriers and facilitators to HIV testing among young men who have sex with men and transgender women in Kingston, Jamaica: a qualitative study' (2017) 20(7) Journal of the International AIDS Society 157.

likelihood to consent to a genetic/ genomic study.[804] The attendees agreed that all human sequence data they produce should be made freely available to the public.

6.4.1 International and regional principles informing data sharing practices

The effort by three international research groups in developing data sharing principles specific to the context of collaborative international genomics research, accompanied by a code of conduct, requires specific mention.[805] These groups are: the international Public Population Project in Genomics (P^3G), an international consortium of projects partaking in large-scale genetic epidemiological studies and biobanks; the European Network for Genetic and Genomic Epidemiology (ENGAGE), a research project aiming to translate data from large-scale epidemiological research initiatives into relevant clinical information; and the Centre for Health, Law and Emerging Technologies (HeLEX). Table 6.1 below is a depiction of the 2011 Code of Conduct developed through the initiatives of the above-cited international consortium. [806]

Table 6.1: The 2011 code of conduct developed by an international consortium

Preamble
This proposed international data sharing Code of Conduct seeks to promote greater access to and use of data in ways that are (as proposed by the joint statement by funders of health research):
Equitable: any approach to the sharing of data should recognize and balance the needs of researchers who generate and use data, other analysts who might want to reuse those data, and communities and funders who expect health benefits to arise from research.
Ethical: all data sharing should protect the privacy of individuals and the dignity of communities, while simultaneously respecting the imperative to improve public health through the most productive use of data.
Efficient: any approach to data sharing should improve the quality and value of research and increase its contribution to improving public health. Approaches should be proportionate and build on existing practice and reduce unnecessary duplication and competition.'
Principles and Procedures
1. Quality
Irrespective of the discipline, scientists involved in data sharing should be *bona fide* researchers.
Proof of academic or other recognized peer reviewed standing is essential.
Harmonization of data collection and archiving methods and tools ensures validation of scientific quality.
Collaboration promotes efficiency, sustainability and comparability.
2. Accessibility

804 Human Genome Organisation (HUGO): Principles Agreed at the First International Strategy Meeting on Human Genome Sequencing: 25-28 February 1996; Bermuda. HUGO; 1996. http://www.gene.ucl.ac.uk/hugo/bermuda.htm accessed 14 September 2020.

805 BM Knoppers, et al, 'Towards a Data Sharing Code of Conduct for International Genomic Research' (2011) 3(7) Genome Med 46.

806 BM Knoppers, et al, 'Towards a Data Sharing Code of Conduct for International Genomic Research' (2011) 3(7) Genome Med 46.

Facilitation of both the deposit of data and secure access to data are the foundations of data sharing.
Curators of databases should promote sharing to generate maximum value.
Harmonization of deposit, access procedures and use promote accessibility, equity and transparency.
3. Responsibility
Responsible governance should be shared between funders, generators and users of data.
Investments in databases require coordination, strategy and long-term core funding.
Mechanisms for building interoperability should be encouraged and appropriate management anticipated.
Capacity building and recognition of all the data generators contributes to best practices.
4. Security
Trust and the promotion of data sharing rely on data management and security mechanisms and also on oversight of their functioning.
Mechanisms for identifying and tracking data generators and users should be international.
5. Transparency
Key policies on publications, intellectual property, and industry involvement should be public.
Websites that are accessible to the general public serve to provide feedback on progress and general results.
6. Accountability
Inter-agency co-operation and funding fosters streamlined and efficient monitoring and good governance.
Provisions should be made for ongoing public engagement that is tailored to the nature of the database and local cultures.
7. Integrity
Mutual respect between all stakeholders is founded on personal and professional integrity.
Prevention of harms and anticipation of public concerns and scientific needs through foresight mechanisms encourage the development of common, prospective policies.
Irresponsible research practices should be reported.
Sanctions for breach of this Code or of other legal or ethical obligations should be clear

The above Code of Conduct is a very useful document to guide researchers involved in data sharing. It is summitted that a code strengthened by an accompanying data sharing agreement, is conducive for sustainably protecting the privacy rights and interests of all parties involved, including research institutions. The above Code is premised on two fundamental values: (i) mutual respect and trust between scientists, stakeholders and participants; and (ii) a commitment to safeguard public trust, participation and investment.

The data privacy legal frameworks[807] in Canada, United States of America, United Kingdom, European Union, Council of Europe and the OECD all acknowledge data sharing policies adopted by major biomedical research funding organisations, such as

807 E Birney, J Vamathevan and P Goodhand, 'Genomics in healthcare: GA4GH looks to 2022' (Bio Rxiv 15 October 2017) https://doi.org/10.1101/203554 accessed 14 September 2020.

the National Institute of Health, Canadian Institutes of Health Research, Genome Canada, and the Wellcome Trust in the context of medical data privacy.[808] Governments globally should encourage genetic testing companies to strive to adhere to relevant laws, regulations, guidelines and principles laid down in international policies from which the NIH[809] and Human Genome Project[810] draw their guidelines.[811]

Principles and guidelines informing genomic research and the protection of research participants find expression in the international and regional documents listed below.[812]

Table 6.2: International and regional documents guiding research and the protection of research participants

• Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (Council of Europe 2005) • Recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin (Council of Europe 2006) • OECD Principles and Guidelines for Access to Research Data from Public Funding (OECD 2007) • International Ethical Guidelines for Epidemiological Studies (CIOMS, WHO (2008) • Recommendations from the 2008 • International Summit on Proteomics Data Release and Sharing Policy (Amsterdam Principles, 2008) • Guidelines for Human Biobanks and Genetic Research Databases (OECD 2008, (2009)	• Constitution of the World Health • WHO Organisation (1946) • Bermuda Principles on Human Genome Sequencing (1996) • Universal Declaration on the Human Genome and Human Rights (UNESCO 1997) • Convention on Human Rights and • Biomedicine (Council of Europe 1997) • Statement on DNA Sampling: Control and Access (HUGO 1998) • Statement on Human Genomic Databases (HUGO Ethics Committee 2002) • Declaration of Ethical Considerations regarding Health Databases (WMA 2002) • International Ethical Guidelines for • Biomedical Research Involving Human Subjects (CIOMS, WHO 2002) • Budapest Open Access Initiative (2002)

808 A Guide for Policy Engagement on Data Protection. 'The Keys to Data Protection' (Privacy International August 2018) https://privacyinternational.org/data-protection-guide accessed 14 September 2020.

809 An agency of the U.S. Department of Health and Human Services, the NIH is the Federal focal point for health and medical research. The NIH website offers health information for the public, scientists, researchers, medical professionals, patients, educators.

810 Human Genome Project began on October 1, 1990 as an inward voyage of discovery led by an international team of researchers looking to sequence and map all of the human genes – together known as the genome**.**

811 'NIH Data Sharing Policy and Implementation Guidance' (Grants 05 March 2003) https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html accessed 14 September 2020.

812 M Jones, K Ankeny, and R Cook-Deegan, 'The Bermuda Triangle: The Pragmatics, Policies, and Principles for Data Sharing in the History of the Human Genome Project' (2018) 51 J Hist Biol 693–805.

• Toronto Statement on Prepublication Data Sharing (2009) • Joint Statement by Funders of Health Research (2011) • 2012 Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Material for Research (ISBER 2012) • Responsible Conduct in the Global (Inter Academy Council 2012) • Declaration of Helsinki (WMA 2013) • Guidelines for the Protection of Privacy and Transborder Flows of Personal Data (OECD 2013)	• Sharing Data from Large-scale Biological Research Projects: A System of Tripartite Responsibility (Fort Lauderdale Statement, 2003) • International Declaration on Human • Genetic Data (UNESCO, IBC 2003) • European Society of Human Genetics: Data Storage and DNA Banking for • Biomedical Research (ESHG 2003) • Universal Declaration on Bioethics and Human Rights (UNESCO 2005)

At the regional level, African countries are increasing their footprint in the biomedical research space. The recognition of the demands for PGx research prompted African countries to implement data protection measures, with the result that several Member States have already ratified the Malabo Convention, which seeks to "optimise unity and show the highest levels of regard for the protection of data". [813] South Africa has become the latest African country to legislate for the protection of personal information.[814]

6.4.2 Data sharing of health information in South Africa

In terms of the NHA, South African "authorised institutions"[815] address the biological material of humans, as well as the data subsequently derived from student training in health science and its advancement through research; therapeutic purposes advanced by means of producing diagnostic, therapeutic, or prophylactic substances;[816] and disclose or keep records of genetic material and other information in any form that is individually identifiable or related to health.[817] These institutions could provide information to health insurers in the event of the written consent of a user (patient) being obtained. [818]

---

813 The African Union member states in 2014 adopted the African Union Convention on Cyber Security and Personal Data Protection, also known as the Malabo convention.

814 Protection of Personal Information Act 4 of 2013.

815 Section 54(1) of the NHA authorises the Minister of Health, by notice in the Gazette, to designate any institution other than an institution contemplated in section 63 as an authorised institution.

816 Section 64(1) of the NHA.

817 Regulation 13, titled "Storage and control of flow of genetic information" in the Regulations Relating to the Use of Human Biological Material (GN R177 in GG 35099 of 2 March 2012).

818 Regulation 13(d), titled "Storage and control of flow of genetic information" in the Regulations Relating to the Use of Human Biological Material (GN R177 in GG 35099 of 2 March 2012).

Insurers of health are permitted by law to legally acquire genetic and health information from institutions that are authorised, which include biobanks that would have acquired the user's or donor's informed consent for the extended storage of genetic material, research findings, or stem cells.[819] It is alarming that this regulation necessitated the anonymity of information that is used for the purposes of research.[820]

In terms of POPIA, genetic and genomic information could be processed lawfully only in the event of a serious medical interest prevailing, or is relevant for statistical, historical or research activity.[821]

6.5 Storage of health information on storage clouds

The storage of personal information on external servers or so-called 'clouds' is also not a simple exercise. Like many health information technology (IT) projects, information grows exponentially to the extent of soliciting additional capacity. Ames[822] maintains that the volume of data on most companies computing systems "…quickly outstripped in-house capabilities in terms of speed and storage capacity".[823] Many data storage facilities switched to Google Cloud at the very beginning of 2017, with Google Cloud ramping up its presence in the life sciences.[824]

Many South Africans' personal information are stored by means of cloud-based services that are provided by commercial platforms that are generally available. In the contemporary era, the ethical and legal ramifications of storing personal information on these clouds still need to be clarified, especially in the light of cloud computing, machine learning and artificial intelligence generally. It seems unrealistic to delink data-dependent work from global commercial platforms and storage clouds.[825] In addition, challenges regarding the exact physical location of data clouds remain

819 Regulation 13(f) "Storage and control of flow of genetic information" in the Regulations Relating to the Use of Human Biological Material (GN R177 in GG 35099 of 2 March 2012).

820 Regulation 13(h) of the regulations above.

821 Sections 32(5)(a) and (b) of the POPIA.

822 M Ames, 'Health Data Compass' https://www.healthdatacompass.org/ accessed 28 October 2020.

823 'Colorado Center for Personalized Medicine Looks to Google Cloud for Data Management' https://cloud.google.com/customers/colorado-center-for-personalized-medicine accessed 28 October 2020.

824 Neil Versel, 'At the Bio-IT World conference in Boston' (Meaningful Hit News 22 June 2017) https://meaningfulhitnews.com/tag/lincoln-weed/ accessed 28 October 2020.

825 M Botes, A Olckers and M Labuschaigne M, 'Data Commercialisation in the South African Health Care Context' (2021) 24 PER / PELJ.

unresolved. [826] However, Bhatia,[827] in defence of cloud services, describes Google Cloud as an important advance in life sciences research,[828] as Google Cloud enables scientists to change the way they perform research and collaborate with one another, even completely remotely.

6.6 Transfer of health information in terms of POPIA

The promotion of open data vis-à-vis protecting personal information in POPIA requires that a delicate balance should be maintained in order to protect the PGx research participant, but not stifle the progress of PGx research. In this regard, research ethics committees (RECs) will play an important role when reviewing research protocols in mitigating the demands of open science with legal privacy protections, to ensure compliance with ethical and legal norms when data is transferred.

The POPIA regulates how personal information is collected, used, stored, shared, and generally processed from the point of collection, until destruction of the information. The POPIA further provides for eight conditions that need to be satisfied when personal information is processed. A research institution or researcher is responsible to ensure that personal information is lawfully processed in accordance with these conditions of POPIA and that participants' Constitutional rights to privacy are not infringed.

National transfers of personal information between institutions require compliance with POPIA, as well as Research Ethics Committee approval and participant consent.[829] International transfers of personal information are regulated by Section 72 of POPIA and may occur under five circumstances, of which the following three are relevant when international transfer for research purposes takes place:

1. when the recipient in the foreign country is legally compliant, compelling corporate protocols or binding agreement providing for a substantial level of protection which

826 Google's 'Project Nightingale' Gathers Personal Health Data on Millions of Americans (The Wall Street Journal 11 November 2019) https://www.wsj.com/articles/google-s-secret-project-nightingale-gathers-personal-health-data-on-millions-of-americans-11573496790 accessed 28 October 2020.

827 K Bhatia (Bio-IT World conference 22 June 2017) https://www.bio-itworldexpo.com/ accessed 05 December 2020.

828 Bhatia maintains that Google cloud is concerned about security and compliance" by offering secure-by-design infrastructure, built-in safeguards, comprehensive identity management, network security, and threat detection and response capabilities".

829 S Mahomed, G Loots and C Staunton, 'The role of Data Transfer Agreements in ethically Managing Data Sharing for Research in South Africa' (2022) 15(1) SAJBL 26-30.

upholds principles that are largely similar for processing personal information in compliance with Section 72(1)(a) of the POPIA.

2. when the participant consents to the transfer in tandem with Section 72(1)(b)); or
3. when the transfer is compliant with the participant's benefit and where consent is not practicable to obtain in a reasonable manner, recognising that if consent was possible, the research participant would likely provide it as stipulated in Section 72(1)(e).

Where the data subject's consent (research participant) is relied upon as a ground for international transfer of personal information for research purposes, this will only be possible where the participant is provided with details of the third party with whom the personal information will be shared, the risks associated with that sharing and the opportunity to withdraw consent at any time (Section 11(2)(b)). However, as withdrawal may not always be possible after the personal information is shared outside South Africa and details of the third party or subsequent risks associated with the sharing may not always be known when the initial consent is obtained, the usefulness of this ground is questionable. Alternately, Section 72(1)(e) indicates that international transfers of personal information may take place where the transfers are for the benefit of each individual participant, which implies that a decision to this effect would need to be made by each individual participant. This ground would almost certainly be impossible as a basis for transfers when large data sets are shared outside South Africa.

Thus, it appears that international transfers are most likely to occur on the grounds of Section 72(1)(a), i.e., when the recipient in the foreign country is legally compliant, compelling corporate rules or binding agreement providing for a substantial level of protection that upholds principles which are sufficiently similar for processing personal information. However, since the Information Regulator has not yet provided guidance on which countries have similar levels of privacy protections as South Africa, or criteria to consider when making such an assessment, a binding contractual agreement for example, a data transfer agreement (DTA), seems to be the most practical solution to safeguard personal information that is shared across borders.[830] Thus, while national transfers of data should take place by complying with the processing requirements as set out in POPIA, Research Ethics Committee approval and in accordance with participant consent; international transfers of data outside South Africa can occur

[830] S Mahomed, G Loots and C Staunton, 'The role of Data Transfer Agreements in ethically Managing Data Sharing for Research in South Africa' (2022) 15(1) SAJBL 26-30.

where there is a binding DTA in place. Amongst setting out the conditions and purposes for which the data will be shared, a DTA should also set out the safety mechanisms in place to protect participant privacy after transfer.

6.7 Data breaches

The risk of data breaches is far-reaching for both individuals and companies, ranging from the loss of control over their personal data, limitation of their rights, discrimination, identity theft or fraud, financial loss, unauthorised reversal of pseudonymisation, damage to reputation, and loss of confidentiality of personal data protected by professional secrecy.[831] For companies, the risks relate to economic or social disadvantage (public embarrassment; stigmatisation), the reputational risks, as well as huge financial impact for affected companies. The IBM Security, which examined the financial impact of data breaches globally, reported that these incidents cost South Africa in 2022 (up to July 2022) around USD 3.6 million in total, or ZAR 55 885 200 million.[832]

More recently, South Africa experienced local health data breaches during the Covid-19 pandemic, such as those reported by Life Healthcare Group, the second largest private hospital operator in South Africa during June 2020;[833] and by Experian, a business and credit information services agency, involving South Africa's biggest data breach ever, exposing the personal information of approximately 24 million South Africans and 793 749 business entities.[834.]An analysis of data breaches between 2015 and 2019, recorded by the Privacy Rights Clearinghouse shows that 76.59% of all recorded data breaches occurred in the healthcare sector, constituting three times as many breaches than those recorded in the education, finance, retail, and government sectors combined. [835] Personal health information is more valuable on the 'black market' than financial data, because hacked health information has a longer shelf-life

831 Examples regarding Personal Data Breach Notification. Guidelines 01/2021 at par 6. https://edpb.europa.eu/system/files/202201/edpb_guidelines_012021_pdbnotification_adopted_en.pdf accessed 2 August 2022.

832 IBM Security, 'Cost of a data breach report 2022' https://www.ibm.com/downloads/cas/XZNDGZKA accessed 2 August 2022.

833 S Mungadze, 'Life Healthcare Reveals Damage Caused by Data Breach' (IT Web, 31 August 2020) https://www.itweb.co.za/content/rW1xLv59YPGvRk6m accessed 2 August 2022.

834 S Mungadze, 'Life Healthcare Reveals Damage Caused by Data Breach' (IT Web, 31 August 2020) https://www.itweb.co.za/content/rW1xLv59YPGvRk6m accessed 2 August 2022.

835 Healthcare Data Breach Statistics, (HIPAA Journal, December 2021) https://www.hipaajournal.com/healthcare-data-breach-statistics/ accessed 2 August 2022.

after the breach, specifically for identity or financial theft. Health care establishments usually have large databases, making them attractive targets for hackers.[836]

6.8 Data protection in the context of PGx in Canada and the United Kingdom

6.8.1 Canada

Canada is a collective economy and health care country where each province has its own set of rules, policies and laws for handling HIV and by extension, management of HIV treatment and ADRs.[837] This has led to diverse responses regarding the handling of the HIV pandemic in each province.[838] English law has been instrumental in the establishing of precedent in respect of medical law and the regulation of biotechnology.[839]

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS), a group focused on incorporating pharmacogenomics into clinical practice, has identified genomic factors responsible for ADRs in certain areas.[840] Clinical practice guidelines have also been created to help clinicians develop better personalized therapy plans based on genomic risk. From a regulatory point of view, pharmacogenomics is yet to be formally regulated, even though recognition of the benefits of PGx is progressively becoming an integral part of the drug discovery and development.[841]

Since PGx necessitates the use of a participant's genes, issues of identifiers in genetic research are a primary consideration.[842] Similar to the situation in South Africa, genetic research and testing for purposes of PGx invoke Constitutional considerations on the protection of personal information, including considerations regarding the rights to dignity, privacy and health care service access.

6.8.1.1 Privacy and data protection in health research

The protection of privacy and confidentiality in Canada follows a complex multi-layered approach, ranging from federal, provincial and sectoral levels. On federal level, two

836 Healthcare Data Breach Statistics, (HIPAA Journal, December 2021) https://www.hipaajournal.com/healthcare-data-breach-statistics/ accessed 2 August 2022.

837 J Robinson, *Information rights Law and Practice* (4 edn Hart Publishing 2014) 66.

838 'What are the rules/laws in Canada that prevent discrimination against HIV/AIDS patients in the workplace?' (*eNotes Editorial* 11 June 2012) https://www.enotes.com/homework-help/what-rules-laws- accessed 13 December 2019.

839 *Hopp v Lepp* (1980) 112 Dominion Law reports(3rd) 67(Sup Ct. Can) and *Bolam v Friern Hospital Management Committee,* 1957)2 All England Reports 118 (Queens Bench Division, High Court).

840 College of Family Physicians (Canada). Pharmacogenetic testing. https://www.cfp.ca/content/66/4/241/tab-article-info accessed 30 November 2022.

841 NOTICE Our file number: 08-108225-127 August 13, 2008 Revision to Guidance Document: Submission of Pharmacogenomic Information.

842 Crolla Domenic, 'Reflections on the Legal, Social, and Ethical Implications of Pharmacogenomic Research' (2006) 46(3) Jurimetrics 239–248.

federal laws apply, namely, the Privacy Act[843] and the Personal Information Protection and Electronic Documents Act (PIPEDA)[844] apply; followed by provincial privacy laws that are either health- or employment related. The Privacy Act links to an individual's right to access and collect personal information that the Government of Canada holds about them. The Act also applies to the Government's collection, use and disclosure of personal information while providing services such as old age security pensions, employment insurance and tax collections, among others. Provinces and territories have their own laws that apply to provincial government agencies and their handling of personal information. For example, some provinces have private-sector privacy laws that apply instead of PIPEDA, whereas others follow health-related privacy laws that have been declared to be substantially similar to PIPEDA. Determining which of the laws are applicable, the following questions are asked:

- Is it a federal government institution?
- What is the nature of the organisation handling the personal information?
- Is it a provincial or territorial government institution?
- Is it private sector?
- Is it engaged in commercial activities?
- Is it a federally regulated business?
- Where is the organisation based?
- What type of information is involved?
- Does the information cross provincial or national borders?[845]

Data protection provisions were also included into the Canadian Human Rights Act in 1982.[846] These laws cover how the federal government handles personal information and they propose some measure of personal protection. Specific to research, the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* is invoked.[847] The above-cited policy statement is a joint policy of Canada's three federal research agencies, namely: the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council of Canada (SSHRC).

---

843 Privacy Act R.S.C., 1985, c. P-21.
844 Personal Information Protection and Electronic Documents Act S.C. 2000, c. 5.
845 Office of the Privacy Commissioner of Canada, https://www.priv.gc.ca/en/privacy-topics/privacy-laws-in-canada/02_05_d_15/ accessed 23 March 2021.
846 Canadian Human Rights Act R.S.C. 1985, c. H-6.
847 Government of Canada 'Research Ethics' (TCPS, 2018) https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2018.html accessed 1 December 2022.

For this thesis, three chapters are important for policy related imperatives: chapter 5, which addresses privacy and confidentiality in research; chapter 12, which concerns the use of human biological material, and also chapter 13, which covers human genetic research, including genetic material banks and gene transfer.

6.8.1.2 Management of adverse drug reactions

As far as the management of ADRs is concerned, the Compliance and Enforcement Policy for Health Products (POL-0001), among others, has an integrated approach to managing the health-related risks and drug products.[848] In addition, the mandate of the Health Products and Food Branch (HPFB) is to monitor health risk factors associated with the efficacy and safety of drugs while maximising the avoidance of ADRs.[849] The HPFB treats all information received as if it were confidential information for purposes of the recently updated Access to Information Act,[850] as well as the Privacy Act,[851] which include among others personal privacy information. The HPFB Guidance Document provides guidance to the federal regulatory authority regarding the evaluation of the safety, efficacy, and quality of available health products.

6.8.1.3 Data sharing in health research

In March 2021, Canada's federal granting agencies, the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Social Sciences and Humanities Research Council of Canada (SSHRC), formally announced the Tri-Agency Research Data Management (RDM) Policy.[852] In order to obtain certain funding for research, applicants will need to submit data management plans (DMPs) with their applications. Although the content and length of DMPs will depend on the research project, all DMPs ought to include a description on the following:

- how data will be collected, documented, formatted, protected and preserved;
- how existing datasets will be used and what new data will be created over the course of the research project;
- whether and how data will be shared; and

---

848 https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products.html accessed 23 March 2021.

849 https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement.html accessed 19 December 2019.

850 Access to Information Act (R.S.C., 1985, c. A-1).

851 Privacy Act, R.S.C. 1985, c. P-21.

852 Government of Canada, 'Tri-Agency Data Management Policy' https://science.gc.ca/site/science/en/interagency-research-funding/policies-and-guidelines/research-data-management accessed 1 December 2022)

- where data will be deposited.[853]

On May 4, 2017, Bill S-201, the Genetic Non-Discrimination Act[854] received Royal Assent. In terms of this Act, no individual may be required to undergo a genetic test or to disclose the existing results of genetic tests. However, once a person agrees to participate in research, this prohibition in the afore-mentioned Act does not apply to a person conducting medical, pharmaceutical or scientific research. Furthermore, the Genetic Non-Discrimination Act does not only prohibit a person to collect, use, or disclose another person's genetic test results without his or her written consent, but also implies that no person will be obliged to disclose a genetic test result to an employer or insurance company or any other business.[855] Once a person agrees to disclose such results, his or her informed consent should be provided in writing.

Despite the Canadian laws on the protection of personal information, the Canadian International Data Sharing Initiative (Can-SHARE) strengthens and expands Canada's leadership role in Big Data sharing through the Global Alliance for Genomics and Health.[856] The sharing of genomic data has also been bolstered by earlier initiatives. The Global Alliance for Genomics and Health (A4GH), for example, is a Canadian based establishment which started in 2013 to encourage collaboration on the development of innovative solutions to accelerate the sharing of genomic and clinical data internationally.[857]

Problems emanating from the different laws include the many databases created in the different provinces of Canada. It is observed in different legislations, provided that possible access to secondary use of data is regulated and limited; as such, retards fair and reasonable global participation and the returns on research investment. Therefore, some institutions may also rely on an Information Sharing Agreement (ISA), where information is shared between institutions inside and outside Canada, or between the Canadian government and foreign governments.[858] The ISA enjoys the status of an

853 Par 3.2 of the Policy. https://science.gc.ca/site/science/en/interagency-research-funding/policies-and-guidelines/research-data-management/tri-agency-research-data-management-policy accessed 1 December 2022.

854 Genetic Non-Discrimination Act S.C. 2017, c. 3.

855 Sections 3 and 4 of the Genetic Non-Discrimination Act.

856 Canadian "Can-Share" is led by P 3 G (the Public Population Project in Genomics and Society), the (GA4GH). Public Population Project in Genomics and Society (P3 G) is a not-for-profit international consortium hosted by the McGill University and Genome Quebec Innovation Centre.

857 Global Alliance for Genomics and Health. Press Release: 10 June 2016. https://www.ga4gh.org/news/#{%22keyword%22:%227%22} accessed 1 December 2022.

858 Government of Canada. Guidance on Preparing Information Sharing Agreements Involving Personal Information. https://www.canada.ca/en/treasury-board-secretariat/services/access-information-privacy/privacy/guidance-preparing-information-sharing-agreements-involving-personal-information.html#Toc267044410 accessed 1 December 2022.

arrangement or agreement or a memorandum of understanding between national and international researchers.

On November 17, 2020, Bill C-11, titled the *Digital Charter Implementation Act* was tabled in the Canadian parliament. This Bill makes major revisions to the *Personal Information Protection and Electronic Documents Act* (PIPEDA) and provides for two new laws, namely: the *Consumer Privacy Protection Act* (CPPA) and the *Personal Information and Data Protection Tribunal Act.*

The PIPEDA contains no specific provisions with respect to cross-border data flows, but only refers to transfers of data to a third party for *processing* only (Clause 4.1.3 of Schedule 1) which requires an organisation responsible for personal information in its possession or custody, including information that has been transferred to a third party for processing, to use contractual or other means to provide a comparable level of protection while the information is being processed by a third party. In other words, transfers are permissible, but the transferring organisation would need to be accountable for the personal data when it is in the hands of the transferee to which the information is transferred. It also places an onus on the transferor to ensure that the information receives a comparable level of protection in the custody of the transferee, by using contracts, for example.

In 2009, the limitations of Clause 4.1.3 in respect of the increased frequency and importance of cross-border data flows resulted in the Office of the Privacy Commissioner of Canada (OPC) issuing guidelines for the processing of personal data across borders. The guidelines also clarify that Canada had adopted an organization-to-organization approach, rather than one that solely focused on the adequacy of the legal regime in the country of transfer, as is the position under POPIA in South Africa.

6.8.2 United Kingdom

Although the advancements in pharmacogenomics (PGx) have convinced researchers in the United Kingdom of the benefits of personalised medicine, the implementation of PGx has not yet found its way into daily clinical practice. The integration and inclusion of the field in routine clinical decision support systems are still very low.

The recent drive initiative to implement genomic medicine into the UK National Health Service (NHS) was largely encouraged by the flourishing of the 100,000 Genomes Project. This Project was a collaboration between research groups in the US, UK, and China and Germany whose intended purpose was to produce an extensive catalogue

of human genetic variation which may assist future medical research studies.[859] Recently, the UK Pharmacogenetics and Stratified Medicine Network, NHS England and Genomics England invited a range of different experts from the health care sector, industry, academia and patient representatives, to discuss the opportunities and challenges of implementing pharmacogenomics in the NHS. This was followed, in 2020 with the launch of the Genome UK strategy,[860] rendering the UK healthcare system the first in the world to offer whole genome sequencing (WGS) as part of routine care. Undoubtedly, the United Kingdom has taken the lead in this regard, compared to South Africa and Canada.

6.8.2.1 Privacy and data protection in health research

As discussed above, PGx requires the sharing of personal information to advance personalised medicine and health care. The European Union (EU) offers a dynamic directive, namely, the General Data Protection Regulation (GDPR),[861] which became effective in 2016 and was directly applicable in all Member States of the EU. On 24th May 2018, a day before the EU-GDPR became effective across Europe, the UK Government approved the updated Data Protection Act, known as Data Protection Act 2018 (DPA 2018).[862] The DPA is a complete revision of the original Data Protection Act of 1998, with relevant provisions from the EU-GDPR incorporated into this legislation, now also known as the UK-GDPR (United Kingdom General Data Act). Protection of personal information of research participants is further complemented by the *UK Policy Framework for Health and Social Care Research* (2017), updated in 2020,[863] that prescribes principles of good practice in the management and conduct of health and social care research in the UK. This policy applies to organisations and individuals that have responsibilities for health and social care research, including funders, sponsors, researchers and their employers, research sites and care providers. In addition, the *Governance Arrangements for NHS Research Ethics Committees: a harmonised edition* (GAfREC)[864] (2011), updated in 2021, provides a standards framework for the ethical review of all NHS and social care research

859 https://www.genome.gov/27528684/1000-genomes-project accessed 1 December 2022.
860 HM Government https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/920378/Genome_UK_-_the_future_of_healthcare.pdf accessed 1 December 2022.
861 General Data Protection Regulation (EU) 2016/679.
862 Data Protection Act 2018 c.12.
863 NHS Health Research Authority, https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/ accessed 1 December 2022.
864 NHS Health Research Authority, https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/ accessed 1 December 2022.

proposals and sets out general standards and principles for an accountable system of Research Ethics Committees (RECs) working collaboratively in respect of shared excellent review standards and operating process throughout the NHS.

6.8.2.2 Management of adverse drug reactions

The UK's health care is governed by the Medicines Act of 1968[865] and the Medicines for Human Use (Marketing Authorisation) Regulations (1994).[866] The Medicines and Health care Regulations Agency (MHRA) is a UK body that requires the licensing of medicines before these may be administered in the health care system. The MHRA monitors and investigates the safety and efficacy of medicines, among other products.

ADRs are reported to the so-called Yellow Card Scheme and are then entered onto a database for the purpose of signal detection. Each week, all drug-reaction combinations in the database are statistically analysed after which a combination is then assigned what is known as a 'disproportionality score'. This score is used to determine drug-reaction combinations that have been reported with suspicious frequently compared to other drug-reaction combinations in the database. Drug-reaction combinations meeting certain criteria are assessed by a group of scientists, physicians and pharmacists to determine whether the 'signal' is medicine-related.[867] The MHRA is also tasked with guiding the UK on pharmacovigilance requirements and the keeping of a register for ADRs.[868]

6.8.2.3 Data sharing in health research

Data sharing in research is guided by different policies and guidelines, depending on the research context. In the context of publicly funded clinical trials, the UKRI (UK Research and Innovation) portal provides guidance in the form of best practices, policies and guidelines on data management, data sharing and data management plans.[869]

In addition, disclosure of information and data security in the UK[870] is regulated by several laws that also safeguard the privacy of research participants. The laws provide

865 Medicines Act of 1968, c.67.
866 Human Use (Marketing Authorisation) Regulations (1994) S.1.1994/3144.
867 MHRA, 'Guidance on adverse drug reactions' https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949130/Guidance_on_adverse_drug_reactions.pdf accessed 1 December 2022.
868 https://www.gmp-compliance.org/gmp-news/brexit-pharmacovigilance-requirements-for-uk-mahs accessed 24 March 2021.
869 UK Research and Innovation, https://www.ukri.org/about-us/mrc/our-policies-and-standards/research/data-management-and-sharing/ accessed 1 December 2022.
870 Article 5(1)(f) of the UK GDPR concerns the 'integrity and confidentiality' of personal data.

for data processing in tandem with the security of data against any untoward incidental damage or loss of personal health information:

- The Personal Information Protection Act[871] (applies to health care providers in private practice);
- The Freedom of Information and Protection of Privacy Act (applies to health authorities and hospitals)[872];
- The E-Health Act or Digital Health Laws and Regulations 2021[873] (applies to certain designated databases);
- The Ministry of Health Act[874] (affords the Minister of Health with the authority to do regulate on personal health information for a wide range of purposes);
- The Public Health Act[875]; and
- The Health Authorities Act[876].

The English health and data protection legislation are to some extent affirmative utilitarian statutes which place a high value on the protection of data. Case law in the UK also accentuates the need for PGx.[877] In some of these laws, it is found that the right to be informed about the collection, usage and disclosure of ones' personal information is tantamount to the given consent, related the right of access to one's personal information.

6.9 Conclusion

This chapter focused fundamentally on the exploration of the legal framework for the protection of personal information in South Africa, Canada and the United Kingdom. This includes a cross-jurisdictional comparison on the regulation of data sharing in health research in these jurisdictions in so far as this relates to PGx.

The discussion shows that the United Kingdom is leading with regard to the clinical implementation of PGx, followed by Canada and South Africa respectively. The picture does not look the same regarding the protection of health information. Following Brexit, data protection and the protection of personal information of research participants are regulated by an intricate hierarchy of laws and policies. Despite a comprehensive data

871 Personal Information Protection Act 2018, c. 12 Data Protection Act.
872 Freedom of Information Act in 2000 and it was brought into force in 2005.
873 https://iclg.com/practice-areas/digital-health-laws-and-regulations/united-kingdom accessed 28 March 2021.
874 Ministry of Health Act 1919, c 2.1.
875 Public Health Act 1961, c.64.
876 Health Authorities Act 1995, c.17.
877 Arron Walthall, 'Legal Pressure to Incorporate Pharmacogenetics in the U.K' (2006) 46(3) Jurimetrics 263-279, 266.

protection law in the form of POPIA in South Africa, many uncertainties regarding the sharing and transferring personal health research information still remains. The legal framework in Canada regarding the protection and sharing of personal information provides more focused guidance, compared to the situation in South Africa and the United Kingdom.

It could be concluded from this chapter that an open science or 'medical information commons' is critically required to promote pharmacogenomic research globally, as well as nationally.[878] It is clear that established laws and principles governing the protection of privacy and confidentiality in health information, including the sharing of, and transferring of health information in all these three jurisdictions, are wholly inadequate to address the complexities that arise from pharmacogenomic research.

Pharmacogenomics research may well be in its infancy globally, but recognition of the benefits of PGx requires that regulators should start to consider developing international guidelines on PGx that may guide national regulators in tailoring national laws along universally recognised principles. One starting point may be to adopt a Code of Conduct for Data Sharing in the context of PGx, ideally endorsed by the World Health Organisation. Realising the rights of PLWH in having access to personalised ARVs could appear distant, but the goal will become much closer when the building blocks to achieve this goal are put into place on an international level.

This thesis acknowledges that there are numerous role players in this context. Therefore, it is imperative that all stakeholders opt for a balanced approach that recognises the interests of the researchers conducting PGx research; the manufacturers of personalised medicine, informed by the PGx research; the distributors of the personalised medicines; physicians prescribing the medicines; as well as the patients, such as PLWH, who will become the recipients/ consumers of the medicines.[879]

Each of the jurisdictions canvassed in this chapter will unavoidably need to review the existing legal regime in order to draft an action plan which facilitates flexibility and openness to change. In the case of South Africa, the drafters of POPIA also advanced the argument that research should be in the best interest of the larger community.[880]

878 R Cook-Deegan and AL McGuire, 'Moving Beyond Bermuda: Sharing Data to Build a Medical Information Commons' (2017) 27(6) Genome Res 897-901.

879 Arron Walthall, 'Legal Pressure to Incorporate Pharmacogenetics in the U.K' (2006) 46(3) Jurimetrics 263-279, 266.

880 B Tata, MS Ambele and M Pepper, 'Barriers to Implementing Clinical Pharmacogenetics Testing in Sub-Saharan Africa' (2020) 12(9) Pharmaceutics 809.

In Canada, the view is that research is plausible for as long as it benefits the Canadian population.[881] Similarly, the UK data protection law follows on the steps of GDPR model which benefits the common good of the British. Based on these scenarios, it could be concluded that these jurisdictions view data sharing and the protection of personal information differently.

The next and final chapter provides an overview of the relevant findings and recommendations proposed in all the chapters in varying levels of detail.

881 Section 30 of the Freedom of Information and Protection of Privacy Act.

Chapter 7

Problems, criticisms, and targeted solutions (recommendations)

7.1 Introduction

Findings emanating from the previous chapters reveal that there are indeed problems, criticisms and targeted solutions concerning the HIV pandemic and its treatment and care. The delicately poised ingenuousness of antiretroviral treatment (ART) brought with it socio-economic and medico-legal problems. An added problem is that of affordability and access to treating people living with HIV (PLWH). The 1993 interim Constitution, as well as Section 27 of the current Constitution of the Republic of South provide that all citizens have the right to access health services. However, this right is limited by affordability (which is intertwined with accessibility) as a national economic constraint. The pith and substance of the thesis is centrally focused on the concepts of pharmacogenetics and pharmacogenomics (PGx). The rationale for such centrality is to establish personalised medicine as the antidote to adverse drug reactions (ADRs).

The current chapter presents and discusses the findings and thereafter propose recommendations to the impact of each harm caused by patent laws, inequitable affordability, accessibility and availability of ARVs in the South African context. Accordingly, alternative or added approach are proposed to the existing laws associated with health issues. Human dignity associated with the protection of personal information should be upheld in all the endeavors to implement PGx as a precursor to the development of personalised medicine in the context of HIV and AIDS.

7.2 Recommendations

The proposed recommendations below are derived entirely from the study's findings, which are themselves integral to both the research problem and aim and objectives of the study.[882]

7.2.1 What type of problems regarding HIV and AIDS epidemic is South Africa faced with?

The HIV pandemic was first announced as a public health threat in the 1980's. However, this pandemic is still prevalent at an international scale, with South Africa being the most affected, as demonstrated by the high 13% rate of occurrence of people living with HIV at 13.0% of the entire population. This translates into approximately 8 eight) million people in 2021, with only an estimated 4.4 million people on antiretroviral

882 SK Grove, Objectives, Questions, Hypothesis, and Study Variables In SK Grove and JR Gray *Burns and Grove's The Practice of Nursing Research: Appraisals, Synthesis, and Generation of Evidence,* (9th edn, Elsevier 2021)

treatments. The transmission of HIV from mothers to their unborn children received special attention via the government's programme of prevention of mother-to-child transmission (PMTCT) of HIV, which has had some successes in recent years, made possible by considerably scaling-up of HIV testing services at antenatal care services. However, despite strides made in this regard to limit the transmission of HIV to unborn children, the Constitutional court judgment that ordered the government to make Nevirapine available to pregnant mothers in public health care settings acknowledged that the potential loss of life was a primary consideration for the court, but that issues regarding safety, efficacy, and resistance to Nevirapine remained that had to be monitored.[883] This thesis argues that the government now needs to move beyond the goal of limiting MTCT of HIV to addressing the emergence of serious ADRs relating to HIV treatment of all PLWH.

Traditionally, pharmacology was intended to produce drugs attributable to the global burden of diseases on the ground of utilitarian common sense as drugs are an indicator of the health care system's viability. As a product of pharmacology, ARVs have been received with apprehension because of issues of efficacy and the safety of these drugs. Secondly, the manufacturing of ARVs as a product of intellectual property has become associated with huge proprietary interests and profit for pharmaceutical companies through patent protection.

The WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) is largely modelled on the international level through the registration of patents. TRIPS is designed to protect IPR by stipulating and providing for and creating an immunity to patent cluster holders. By extension, TRIPS also provides rules of enforcement to protect patent-holders, strongly held by especially USA pharmaceutical companies. Patent laws are fundamentally designed to protect IPR and primarily offer mass production of drugs with a limited essential consideration for the individual reception of the drug (safety and efficacy).

This thesis has discussed some of the adverse inferences drawn from responses of high-income countries implicated in the epic ARV patent controversies and the pricing of HIV drugs. Affordability, accessibility, and availability of ARVs in the South African context were significantly affected by the pricing of ARVs globally, impacting on the right of access to health care services of PLWH. The emergence of adverse drug

883 Minister of Health and Others v Treatment Action Campaign and Others (No 2) (CCT8/02) [2002] ZACC 15; 2002 (5) SA 721 (CC); 2002 (10) BCLR 1033 (CC) (5 July 2002) par [131].

reactions (ADRs) regarding ARVs, especially by PLWH, necessitated a critical stance by the South African government, not only regarding issues of affordability and accessibility of the ARVs, but more recently regarding the safety and efficacy of the ARVs. Developments in the fields of pharmacogenetics and pharmacogenomics (PGx) have shown to hold a lot of promise in releasing the inherent tension between the protection of IPR by pharmaceutical manufacturers and the right of access to health care for PLWH. Sadly, the South African government's initial response to HIV was one of denialism, which significantly delayed the recognition of HIV and its treatment, leading to the unnecessary loss of many lives. Fortunately, as a result of the efforts of civic groups, notably the TAC, important changes were made that would improve access to and affordability of ARVs to PLWH. Despite this small victory, the lack of sufficient state resources in the health care sector was a turning point on which the landmark judgment in the *Soobramoney* case was decided. The Constitutional court made it clear that the state was no more required than to give effect to the right of access to health care services in Section 27 of the Constitution in a progressive manner as far as available resources would permit. Broadly seen, prospects of the pursuing PGx against this background would appear dim. As this thesis has attempted to show, the serious and often life-threatening range of ADRs associated with the bulk manufactured ARVs, can only be tempered by the development of personalised medicine, whose manufacturing is tailored to the specific genetic traits and profile of specific individuals and groups. Personalised medicine is the product and goal of pharmacogenomics and -genomic research (PGx).

7.2.2 What impact will be brought about by the implementation of PGx?

The manufacturing of ARVs came as a one-size-fits-all type of treatment to PLWH. This thesis explored the phenomenon of adverse drug reactions (ADRs) caused by the diversity in human enzyme's response to drugs. PGx invokes the use of genetics to unravel the diversity in human response to drugs. The focus on the role of genetics in the development of medicine requires flexible and state of the art laws and policies to ensure that personalised medicine is manufactured in a legal framework that regulates not only the removal, use, processing and transfer of human biological material, but one that ensures that biobanks and research with human biological material, which includes genetic material, is carefully regulated in a manner that respects the human rights of PLWH, and follows proper clinical trial processes under the prescribed ethico-regulatory oversight mechanisms provided for in the NHA and Medicines Act. The protection of personal information requires specific attention, as genetic information reveals very unique and personal information relating to

individuals, their families, and specific communities. Possible stigmatisation, prejudice and discrimination should pre-emptively be addressed, not only in the health care context, but also in the contexts of employment, education, insurance, to name but a few.

A comparative analysis of existing regulatory approaches to the PGx in South Africa, the UK and Canada shows that progress towards the implementation of PGx has been slow, due to several factors, most important of which relate to issues of affordability, available resources, as well as human capacity building, requiring specialised training of the relevant medical personnel.

The thesis also identified a delayed appreciation and application of PGx as a concept and a health care science in health research in South Africa. Whilst arguments regarding financial constraints in the public sector are put forward to curb PGx efforts, private health research collaborations are able to take firm strides in pushing the PGx agenda. Therefore, the identified gaps in the South African health care framework need to be closed as soon as possible in order to pave the way for PGx to be pursued without any unnecessary impediments.

7.2.3 How is personal information protected in the implementation of PGx and the development of personalised medicine?

A variety of ART drug therapies are currently available by prescription for PLWH. It takes funding to conduct a clinical trial, and the involved scientists often expect some form of reward (academic or otherwise) for their scientific effort. Moreover, participants who offer their human biological material (specimen), must do so altruistically. Their only reward is universal philanthropic gain. Health researchers in South Africa conduct research under ethico-regulatory oversight where human biological material is removed and used in research. Because genetic material holds very personal information, the sharing of biological samples and information derived from the samples require the participants' informed consent for the further use and transfer of both the samples and the data in terms of health legislation and legislation protecting personal information. Further down-stream commercialisation of human biological products may become eligible for patent protection, leading to additional exclusionary protection in favour of patent holders to the exclusion of the research participant.

Two reasons are advanced for the existing disparity between public interest and the exclusivity of rights when faced with the legal protection of personal information, resourcefulness of governments and knowledgeable scientists against participants in

indigent and HIV-plagued LMICs. Health research scientists and research and the ART drug manufacturers should prioritise the alleviation of adverse drug reactions by promoting PGx on a global and national level. The pursuit of PGx requires a fine balance to be struck between a range of competing interests and priorities, necessitating collaboration of some kind.

7.2.4 Should collaboration be a requirement?

From the comparative country analysis in Chapter 5, it is evident that antecedent laws and the provision of databases should guide the researchers' PGx approaches, which refers to the establishment of databases consisting of data following the genetic profiling of individuals or groups benefiting from the ART. This thesis suggests that the Human Genome Project may play a pivotal role in this regard and that a call for collaboration from HICs and LMICs across the globe should be made for input on a universal and open-access genome database consisting of the widest possible range of both exome and genome sequencing data from a wide variety of large-scale sequencing projects, making summary data available for the wider scientific community. An inference drawn from the Covid-19 pandemic is the diverse responses by different individuals or groups to the strength, composition, dosage as well as the physical metabolic assimilation of the vaccine. The same applies to PLWH who encounter opportunistic diseases that may require a combination of medicines to be administered, each of which serves a unique purpose, but jointly work to accomplish several important goals.

PGx requires specific genetic testing tools to be incorporated into clinical practice. A bedside testing tool is recommended, because medication is can then be offered in a medical health facility where prompt observation of the patient is enabled. The results obtained from the bedside tool should be stored in a database for future reference. Another recommendation for the facilitation of PGx is a clinical setting consultation where blood and other specimens are obtained to establish the ailment as well as the prescription for appropriate treatment. It is in such instances that a treating doctor can access the database created by the Human Genome Project, as well a hospital facility database where the application of algorithms is made possible.

Based on the existence of the readily accessible databases in respect of PGx, the patient's information requires utmost protection to assure the protection of his or her right to dignity, privacy and confidentiality. All the relevant stakeholders in the facilitation of PGx need to be aware of the existing laws and regulations designed to protect personal information.

After canvassing the way protection of information is legislated in the selected jurisdictions, the thesis recommends the development of a common applicable legal structure, responsible for developing international guidelines on PGx that may guide national regulators in tailoring national laws along universally recognised principles. One starting point may be to adopt a Code of Conduct for Data Sharing in the context of PGx, ideally endorsed by the World Health Organisation. Acknowledging that the rights of PLWH in having access to personalised ARVs may appear a pipe dream at this juncture in time, this goal will become more attainable when the building blocks to achieve this goal are put into place on a global level.

Finally, it is submitted that the research question posed in this thesis, which postulates that the adverse drug reactions associated with patented ARVs infringes on the rights of PLWH, in addition to posing serious health and safety risks and negative side-effects, may be answered in the affirmative. Furthermore, I believe that the thesis has convincingly illustrated that the implementation of PGx and the development of personalised medicine in the context of the development of ARVs for PLWH should be prioritised by the South African government, not only to alleviate the burden of ADRs experienced by PLWH, but to give effect to the right of PLWH to have access to health care services that are safe and effective, thereby prolonging the quality of their lives in a manner that also supports their rights to human dignity, equality, and privacy. Implementing this priority would require a revision to the existing legal framework to better guide PGx research and the development of personalised medicine in a safe and responsible manner, guided by relevant ethical, legal, and social considerations.

8 Bibliography

8.1 Books

Andersen SK, *et al, EHealth Beyond the Horizon – Get IT There*

Andersen SK, *et al, EHealth Beyond the Horizon – Get IT There* (IOS Press 2008)

Flick U, *Introducing Research Methodology*,

Flick U, *Introducing Research Methodology*, (3rd Edn Sage, 2020).

Bennett PN and Brown MJ, *Clinical Pharmacology*

Bennett PN and Brown MJ, *Clinical Pharmacology* (9 Edn McGraw-Hill Medical 2003)

Bin R, Lorenzon S and Lucchi N, *Pharmacogenetics and Fundamental Rights*

Bin R, Lorenzon S and Lucchi N, *Pharmacogenetics and Fundamental Rights* (Milan New York 2012)

Carstens P and Pearmain P *Foundational Principles of the South African Medical Law*

Carstens P and Pearmain P *Foundational Principles of the South African Medical Law* (Lexis Nexis 2007)

Cohen G, *et al, Big Data, Health Law, and Bioethics*

Cohen G, *et al, Big Data, Health Law, and Bioethics* (Cambridge University Press 2018)

Cook T, *A User's Guide to Patents*

Cook T, *A User's Guide to Patents* (2 Edn Tottel Publishers 2008)

Daunton M, Narlikar A and Stern R, *The Oxford Handbook on The World Trade Organization*

Daunton M, Narlikar A and Stern R, *The Oxford Handbook on The World Trade Organization* (Oxford University Press 2012)

Dickenson D, *Me Medicine vs We Medicine: Reclaiming Biotechnology for the Common Good*

Dickenson D, *Me Medicine vs We Medicine: Reclaiming Biotechnology for the Common Good* (Columbia University Press 2013)

Dhai A and McQuoid-Mason D, *Bioethics, Human Rights and Health Law Principles*

Dhai A and McQuoid-Mason D, *Bioethics, Human Rights and Health Law Principles and Practice* (Juta 2011)

Everard M, *Drugs and Money - Prices, Affordability and Cost Containment*

Everard M, *Drugs and Money - Prices, Affordability and Cost Containment* (IOS Press 2003)

Grove S, *Objectives, Questions, Hypothesis, and Study Variables*

Grove, SK Objectives, Questions, Hypothesis, and Study Variables (pp. 129-150). In Grove, SK and Gray, JR, *Burns and Grove's The Practice of Nursing Research: Appraisals, Synthesis, and Generation of Evidence,* 9th ed. Missouri: Elsevier 2021.

Helbig S and Harman LB, *Ethical Challenges in the Management of Health Information*

Helbig S and Harman LB, *Ethical Challenges in the Management of Health Information* (2 Edn Jones Bartlett Publishers Canada 2006)

Kiliç B, *Boosting Pharmaceutical Innovation in the Post-TRIPS Era- Real-Life Lessons for the Developing World*

Kiliç B, *Boosting Pharmaceutical Innovation in the Post-TRIPS Era- Real-Life Lessons for the Developing World* (Edward Elgar Publishing Limited 2014)

Jackson W, *The Genealogy of a Gene Patents, HIV/AIDS and Race*

Jackson W, *The Genealogy of a Gene Patents, HIV/AIDS and Race* (Cambridge MA: The MIT Press 2015)

Jamison D, *Disease Control Priorities in Developing Countries*

Jamison D, *Disease Control Priorities in Developing Countries* (Oxford University Press 2006)

Lessig L, *The Future of Ideas the Fate Of the Commons in a Connected World*

Lessig L, *The Future of Ideas the Fate Of the Commons in a Connected World* (Random House New York 2001)

MacLeod C, *Inventing the Industrial Revolution: The English Patent System*

MacLeod C, *Inventing the Industrial Revolution: The English Patent System* (Cambridge University Press 1988)

Matsushita, *et al, The World Trade Organization: Law, Practice and Policy*

Matsushita, *et al, The World Trade Organization: Law, Practice and Policy* (2 Edn Oxford International Law Library 2006)

MDGs, *Health and Development Policy, Health and the Millennium Development Goals*

MDGs, *Health and Development Policy, Health and the Millennium Development Goals* (World Health Organisation 2005)

Muller G, *Troubled Relationships Under the GATS: Tensions between Market Access (Article XVI, National Treatment (Article XVII) and Domestic Regulations (Article VI)*

Muller G, *Troubled Relationships Under the GATS: Tensions between Market Access (Article XVI, National Treatment (Article XVII) and Domestic Regulations (Article VI)* (Cambridge University Press 2017)

Pogge T, *World Poverty and Human Rights*

Pogge T, *World Poverty and Human Rights* (2 Edn Cambridge UK Polity Press 2008)

Rick Turner, *New Drug Development an Introduction to Clinical Trials*

Rick Turner, *New Drug Development an Introduction to Clinical Trials* (2 Edn Springer Verlag New York 2010)

Rodrigues EB, *The General Exception Clauses of the TRIPS Agreement*

Rodrigues EB, *The General Exception Clauses of the TRIPS Agreement* (2012, United Kingdom Cambridge University Press 2012)

Samuels P and Nordhaus W, *Economics*

Samuels P and Nordhaus W, *Economics* (13 Edn McGraw Hill 1989)

Schellack G, *Pharmacology in Clinical Practice - Application Made Easy for Nurses and Allied Health Professionals*

Schellack G, *Pharmacology in Clinical Practice - Application Made Easy for Nurses and Allied Health Professionals* (2 Edn Juta Books 2010)

Singhal A and Howard WS, *The Children of Africa Confront AIDS from Vulnerability to Possibility*

Singhal A and Howard WS, *The Children of Africa Confront AIDS from Vulnerability to Possibility* (Ohio University Press 2003)

Smith R, *et al, A Handbook of International Trade in Services*

Smith R, *et al, A Handbook of International Trade in Services* (Oxford University Press 2008)

Trebilcock MJ, *Advanced Introduction to International Trade Law*

Trebilcock MJ, *Advanced Introduction to International Trade Law* (Edward Elgar Publishing 2015)

Turner RJ, *New Drug Development an Introduction to Clinical Trials*

Turner RJ, *New Drug Development an Introduction to Clinical Trials* (2 Edn Springer Verlag New York 2010)

Virashmee Ramdial *A Minimum Core Content to The Right to Health for HIV Positive Persons Under South Africa's Transformative Constitution*

Virashmee Ramdial *A Minimum Core Content to The Right to Health for HIV Positive Persons Under South Africa's Transformative Constitution* (LLM Thesis, University of Kwa-Zulu Natal 2014)

Wenger R, *et al, Core Curriculum for Primary Care Pediatric Nurse Practitioners*

Wenger R, *et al, Core Curriculum for Primary Care Pediatric Nurse Practitioners* (Mosby 2006)

Wyne A, *et al, Pharmacotherapeutics for Nurse Practitioner Prescribers*

Wyne A, *et al, Pharmacotherapeutics for Nurse Practitioner Prescribers* (2 Edn FA Davis Company 2007)

8.2 Journal articles

Akkari ACS, *et Al*, 'Pharmaceutical Innovation: Differences between Europe, USA and Pharmerging Countries'

Akkari ACS, *et Al*, 'Pharmaceutical Innovation: Differences between Europe, USA and Pharmerging Countries' (2016) 23(2) Gest Prod

Alomar MJ, 'Factors Affecting the Development of Adverse Drug Reactions'

Alomar MJ, 'Factors Affecting the Development of Adverse Drug Reactions' (2014a) 22(2) Saudi pharmaceutical journal 83

Anderson RM, May RM and Mclean AR, 'Possible Demographic Consequences of AIDS in Developing Countries'

Anderson RM, May RM and Mclean AR, 'Possible Demographic Consequences of AIDS in Developing Countries' (1988) 332(6161) Nature 228

Attaran A and Gillespie-White L, 'Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?'

Attaran A and Gillespie-White L, 'Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?' (2001) 286(15) JAMA 1886-1892

Baker BK, 'Patents, Pricing, and Access to Essential Medicines in Developing Countries'

Baker BK, 'Patents, Pricing, and Access to Essential Medicines in Developing Countries' (2009) 11(7) AMA Journal of Ethics 527

Baker DB, Kaye J and Terry SF, 'Governance through Privacy, Fairness, and Respect for Individuals'

Baker DB, Kaye J and Terry SF, 'Governance through Privacy, Fairness, and Respect for Individuals' (2016) 4(2) eGEMs

Baker JL, *et al,* 'Pharmacogenomic Implications of the Evolutionary History of Infectious Diseases in Africa'

Baker JL, *et al,* 'Pharmacogenomic Implications of the Evolutionary History of Infectious Diseases in Africa' (2017) 17(2) The pharmacogenomics journal 112

Baleta A, 'South Africa to Redouble Efforts to Control the Spread of HIV'

Baleta A, 'South Africa to Redouble Efforts to Control the Spread of HIV' (1999) 354(9181) The Lancet 844

Bayat A, ‘Bioinformatics (Science, Medicine, and the Future)’

Bayat A, ‘Bioinformatics (Science, Medicine, and the Future) (2002) 324(7344) BMJ 1018-1022

Bentley DR, ‘The Human Genome Project—An Overview’

Bentley DR, ‘The Human Genome Project—An Overview' (2000) 20(3) Med Res Rev 189

Birbal S, *et al,* 'Adverse Drug Reactions Associated with Antiretroviral Therapy in South Africa'

Birbal S, *et al,* 'Adverse Drug Reactions Associated with Antiretroviral Therapy in South Africa' (2016) 15(3) African Journal of AIDS Research 243

Blaskiewicz R, 'The Big Pharma Conspiracy Theory’

Blaskiewicz R, 'The Big Pharma Conspiracy Theory' (2013) 22(4) Medical Writing 259

Blood, German Advisory Committee, 'Human Immunodeficiency Virus (HIV)'

Blood, German Advisory Committee, 'Human Immunodeficiency Virus (HIV)' (2016) 43(3) Transfusion Medicine and Hemotherapy 203

Cacabelos R, Cacabelos N and Carril CJ, 'The Role of Pharmacogenomics in Adverse Drug Reactions'

Cacabelos R, Cacabelos N and Carril CJ, 'The Role of Pharmacogenomics in Adverse Drug Reactions' (2019) 12(5) Expert review of clinical pharmacology 407

Campbell Y, Omobolaji T and Gandhi TR, 'Update on Human Immunodeficiency Virus (HIV)-2 Infection'

Campbell Y, Omobolaji T and Gandhi TR, 'Update on Human Immunodeficiency Virus (HIV)-2 Infection' (2011) 52(6) Clinical infectious diseases 780

Chawla A, *et al,* 'A Review of Long-Term Toxicity of Antiretroviral Treatment Regimens and Implications for an Aging Population'

Chawla A, *et al,* 'A Review of Long-Term Toxicity of Antiretroviral Treatment Regimens and Implications for an Aging Population' (2018) 7(2) Infect Dis Ther 183–195

Chigwedere P, *et al*, 'Estimating the lost Benefits of Antiretroviral Drug use in South Africa'

Chigwedere P, *et al*, 'Estimating the lost Benefits of Antiretroviral Drug use in South Africa' (2008) 49(4) JAIDS J Acquired Immune Defic Syndromes 410

Cohen, Jonathan and Ezer, 'Human Rights in Patient Care: A Theoretical and Practice Framework'

Cohen, Jonathan and Ezer, 'Human Rights in Patient Care: A Theoretical and Practice Framework' (2013) 15 Health & Human Rights 7

Coleman JJ and Pontefract SK, 'Adverse Drug Reactions'

Coleman JJ and Pontefract SK, 'Adverse Drug Reactions' (2016) 16(5) Clinical Medicine 481

Collins FS and McKusick VA, 'Implications of the Human Genome Project for Medical Science'

Collins FS and McKusick VA, 'Implications of the Human Genome Project for Medical Science' (2001) 285(5) JAMA 540.

Correa CM, 'Flexibilities Provided by the Agreement on Trade-Related Aspects of Intellectual Property Rights'

Correa CM, 'Flexibilities Provided by the Agreement on Trade-Related Aspects of Intellectual Property Rights' (2018) 96(3) Bull World Health Organ 148

Dandara C, *et al*, 'African Pharmacogenomics Consortium: Consolidating Pharmacogenomics Knowledge, Capacity Development and Translation in Africa: Consolidating Pharmacogenomics Knowledge, Capacity Development and Translation in Africa'

Dandara C, *et al*, 'African Pharmacogenomics Consortium: Consolidating Pharmacogenomics Knowledge, Capacity Development and Translation in Africa: Consolidating Pharmacogenomics Knowledge, Capacity Development and Translation in Africa' (2019) 2 AAS open research

Davis DM, 'How Studying the Immune System Leads us Tto New Medicines'

Davis DM, 'How Studying the Immune System Leads us Tto New Medicines' (2018) 391(10136) The Lancet 2205

Detmer DE and Steen EB, 'The Computer-Based Record: Patient Moving from Concept Toward Reality'

Detmer DE and Steen EB, 'The Computer-Based Record: Patient Moving from Concept Toward Reality' (1996) 42(1-2) Int J Biomed Comput 9

Diaz-Papkovich A, *et al*, 'UMAP Reveals Cryptic Population Structure and Phenotype Heterogeneity in Large Genomic Cohorts'

Diaz-Papkovich A, *et al*, 'UMAP Reveals Cryptic Population Structure and Phenotype Heterogeneity in Large Genomic Cohorts' (2019) 15(11) PLoS genetics

Eddy DM, 'Evidence-Based Medicine: A Unified Approach'

Eddy DM, 'Evidence-Based Medicine: A Unified Approach' (2005) 24(1) Health Aff 9

Eisenfeld J and Serres F, 'African Legal Developments in the United States and Sub-Saharan Africa'

Eisenfeld J and Serres F, 'African Legal Developments in the United States and Sub-Saharan Africa' (2001) The International Lawyer 869

Gates AJ, *et al*, ‘A Wealth of Discovery Built on the Human Genome Project by the Numbers’

Gates AJ, *et al*, ‘A Wealth of Discovery Built on the Human Genome Project by the Numbers’ (2021) 590(7845) Nature 212-215

Gilks CF, *et al*, 'The WHO Public-Health Approach to Antiretroviral Treatment against HIV n Resource-Limited Settings'

Gilks CF, *et al*, 'The WHO Public-Health Approach to Antiretroviral Treatment against HIV n Resource-Limited Settings' (2006) 368(9534) The lancet 505

Goldman BR, 'Pharmacogenomics: Privacy in the Era of Personalized Medicine'

Goldman BR, 'Pharmacogenomics: Privacy in the Era of Personalized Medicine' (2005) 4 Nw J tech & intel prop 83

Gray A, Suleman F and Pharasi B, 'South Africa’s National Drug Policy: 20 years and still going?’

Gray A, Suleman F and Pharasi B, 'South Africa’s National Drug Policy: 20 years and still going?' (2017) 2017(1) South African Health Review 49

Grootboom, Mzukisi and Sonderup, 'A Reflection on the South African Medical Association-Past, Present and Future'

Grootboom, Mzukisi and Sonderup, 'A Reflection on the South African Medical Association-Past, Present and Future' (2014) 104(6) SAMJ: South African Medical Journal 408

Haakonsson SJ and Richey LA, 'TRIPs and Public Health: The Doha Declaration and Africa'

Haakonsson SJ and Richey LA, 'TRIPs and Public Health: The Doha Declaration and Africa' (2007) 25(1) Development policy review 71

Haga SB and Moaddeb J, 'Comparison of Delivery Strategies for Pharmacogenetic Testing Services'

Haga SB and Moaddeb J, 'Comparison of Delivery Strategies for Pharmacogenetic Testing Services' (2014) 24(3) Pharmacogenetics and genomics 139

Härmark L and Van Grootheest AC, 'Pharmacovigilance: Methods, Recent Developments and Future Perspectives'

Härmark L and Van Grootheest AC, 'Pharmacovigilance: Methods, Recent Developments and Future Perspectives' (2008) 64(8) Eur J Clin Pharmacol 743

Hopkins KL, Doherty T and Gray GE, 'Will the Current National Strategic Plan Enable South Africa to end AIDS, Tuberculosis and Sexually Transmitted Infections by 2022?'

Hopkins KL, Doherty T and Gray GE, 'Will the Current National Strategic Plan Enable South Africa to end AIDS, Tuberculosis and Sexually Transmitted Infections by 2022?' (2018) 19(1) Southern African journal of HIV medicine

Huddart S, *et al,* 'The Doha Declaration in Action: An Examination of Patent Law Flexibilities in the South African Acquired Immunodeficiency Syndrome Epidemic'

HuddartS, *et al,* 'The Doha Declaration in Action: An Examination of Patent Law Flexibilities in the South African Acquired Immunodeficiency Syndrome Epidemic' (2017b) 5(1) Journal of Health Specialties 30

Johnson KA, *et al,* 'Automated Medical Algorithms: Issues for Medical Errors'

Johnson KA, *et al,* 'Automated Medical Algorithms: Issues for Medical Errors' (2002) 9(Supplement_6) Journal of the American Medical Informatics Association 56

Jonker DM, *et al*, 'Towards a Mechanism-Based Analysis of Pharmacodynamic Drug–Drug Interactions in Vivo'

Jonker DM, *et al*, 'Towards a Mechanism-Based Analysis of Pharmacodynamic Drug–Drug Interactions in Vivo' (2005) 106(1) Pharmacol Ther 1

Kalman LV, *et al*, 'Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting'

Kalman LV, *et al*, 'Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting' (2016) 99(2) Clinical Pharmacology & Therapeutics 172.

Keppler H, 'The untold AIDS Story: How Access to Antiretroviral Drugs was Obstructed in Africa'

Keppler H, 'The untold AIDS Story: How Access to Antiretroviral Drugs was Obstruced in Africa' (2013)

Knoppers BM, *et al*, 'Towards a Data Sharing Code of Conduct for International Genomic Research'

Knoppers BM, *et al*, 'Towards a Data Sharing Code of Conduct for International Genomic Research' (2011) 3(7) Genome Medicine 1

Kramer, E ‘No one may be Refused Emergency Medical Treatment' - Ethical Dilemmas in South African Emergency Medicine’

Kramer, E ‘No one may be Refused Emergency Medical Treatment' - Ethical Dilemmas in South African Emergency Medicine’ (2008) 1(2) South African Journal of Bioethics and Law 53-56.

Kumar M, *et al*, 'Pharmacovigilance and its importance in Drug Regulation: An Overview'

Kumar M, *et al*, 'Pharmacovigilance and its importance in Drug Regulation: An Overview' (2011) 3(2) Der Pharmacia Lettre 165

Lander ES, et al, 'Initial Sequencing and Analysis of the Human Genome'

Lander ES, et al, 'Initial Sequencing and Analysis of the Human Genome' (2001)

Langlois A, ‘The UNESCO Bioethics Programme’

Langlois A, ‘The UNESCO Bioethics Programme’ (2014) 20(1) The New Bioethics 3-11

Le Quintrec JS and Le Quintrec JL, 'Drug-Induced myopathies'

Le Quintrec JS and Le Quintrec JL, 'Drug-Induced myopathies' (1991) 5(1) Baillieres Clin Rheumatol 21

Leandro JA, 'Risk-free Rest and Sleep: Jornal do Médico (Portugal) and the Thalidomide Disaster, 1960-1962'

Leandro JA, 'Risk-free Rest and Sleep: Jornal do Médico (Portugal) and the Thalidomide Disaster, 1960-1962' (2020) 27 História, Ciências, Saúde-Manguinhos 15

Leisinger*, et al*, 'Improving Access to Medicines in Low and Middle Income Countries: Corporate Responsibilities in Context'

Leisinger*, et al*, 'Improving Access to Medicines in Low and Middle Income Countries: Corporate Responsibilities in Context' (2012) 5(2) Southern med review 3

Lorie, Graham and Stephen, ‘Intellectual Property’s First Sale Doctrine and the Policy Against Restraints on Alienation’

Lorie, Graham and Stephen, “Intellectual Property’s First Sale Doctrine and the Policy Against Restraints on Alienation” (2020) 7(3) 7 Tex. A&M Law Review 497

Mahnke YD, *et al*, 'Reconstitution of Peripheral T cells by Tissue-Derived CCR4 Central Memory Cells following HIV-1 Antiretroviral Therapy'

Mahnke YD, *et al*, 'Reconstitution of Peripheral T cells by Tissue-Derived CCR4 Central Memory Cells following HIV-1 Antiretroviral Therapy' (2016) 1(2) Pathogens & immunity 260

Maimela C, 'Does the Right to Access to Health Care Services in terms of Section 27 of the Constitution of South Africa, 1996 Cater for Cancer Patients?'

Maimela C, 'Does the Right to Access to Health Care Services in terms of Section 27 of the Constitution of South Africa, 1996 Cater for Cancer Patients?' (2018) 39(1) Obiter 1

Marshall A, 'Getting the Right Drug into the Right Patient'

Marshall A, 'Getting the Right Drug into the Right Patient' (1997) 15(12) Nat Biotechnol 1249

Matimba, Dhoro and Dandara, 'Is there a Role of Pharmacogenomics in Africa'

Matimba, Dhoro and Dandara, 'Is there a Role of Pharmacogenomics in Africa' (2016) 1 Global health, epidemiology and genomics

Mayor S, 'GlaxoSmithKline Licenses Production of Generic AIDS Drugs in South Africa'

Mayor S "GlaxoSmithKline Licenses Production of Generic AIDS Drugs in South Africa" (2001) 323(7317) BMJ 828

Merson M, *et al,* 'The History and Challenge of HIV Prevention'

Merson M, *et al,* 'The History and Challenge of HIV Prevention' (2008) 372(9637) The Lancet 475

Michaud V, *et al*, 'The Dual Role of Pharmacogenetics in HIV Treatment: Mutations and Polymorphisms Regulating Antiretroviral Drug Resistance and Disposition'

Michaud V, *et al*, 'The Dual Role of Pharmacogenetics in HIV Treatment: Mutations and Polymorphisms Regulating Antiretroviral Drug Resistance and Disposition' (2012) 64(3) Pharmacol Rev 803

Miko I, 'Genetic Dominance: Genotype-Phenotype Relationships'

Miko I, 'Genetic Dominance: Genotype-Phenotype Relationships' (2008) 1(1) Nature Education 140

Mkwanazi N*, et al*, 'Rapid Testing may not Improve uptake of HIV Testing and same day results in a rural South African community: a cohort study of 12,000 women'

Mkwanazi N*, et al*, 'Rapid Testing may not Improve uptake of HIV Testing and same day Results in a Rural South African community: a cohort study of 12,000 women' (2008) 3(10) PLoS One

Mulwa LS and Marc S, 'Antiviral Compounds from Myxobacteria'

Mulwa LS and Marc S, 'Antiviral Compounds from Myxobacteria' (2018) 6(3) Microorganisms 73

Mwisongo A, *et al*, 'The Quality of Rapid HIV Testing in South Africa: An Assessment of Testers' Compliance'

Mwisongo A, *et al*, 'The Quality of Rapid HIV Testing in South Africa: An Assessment of Testers' Compliance' (2016) 16(3) African health sciences 646

Nakagawa F, *et al*, 'Projected Lifetime Healthcare Costs Associated with HIV Infection'

Nakagawa F, *et al*, 'Projected Lifetime Healthcare Costs Associated with HIV Infection' (2015b) 10(4) PloS One

Nguyen NQ, 'Parallel Trade of Patented Pharmaceuticals: A Discussion from Developing Country Perspective'

Nguyen NQ, 'Parallel Trade of Patented Pharmaceuticals: A Discussion from Developing Country Perspective' (2011) Parallel Trade of Patented Pharmaceuticals: A Discussion from Developing Country Perspective (February 23, 2011)

Olsson S, Shanthi N and Dodoo A, 'Pharmacovigilance in Resource-Limited Countries'

Olsson S, Shanthi N and Dodoo A, 'Pharmacovigilance in Resource-Limited Countries' (2015) 8(4) Expert review of clinical pharmacology 449

Ping A and Winkler CA, 'Host Genes Associated With HIV/AIDS: Advances in Gene Discovery'

Ping A and Winkler CA, 'Host Genes Associated With HIV/AIDS: Advances in Gene Discovery' (2010b) 26(3) Trends in genetics 119

Pirmohamed M, 'Pharmacogenetics and Pharmacogenomics'

Pirmohamed M, 'Pharmacogenetics and Pharmacogenomics' (2001c) 52(4) Br J Clin Pharmacol 345

Pogge, Thomas, 'World Poverty and Human Rights'

Pogge, Thomas, 'World Poverty and Human Rights' (2005) 19(1) Ethics & international affairs 1

Pufall E, *et al*, 'Sexualized Drug use (‘chemsex’) and High-Risk Sexual Behaviours in HIV-Positive Men who have Sex with Men'

Pufall E, *et al*, 'Sexualized Drug use (‘chemsex’) and High-Risk Sexual Behaviours in HIV-Positive Men who have Sex with Men' (2018) 19(4) HIV medicine 261

Rahalkar, *et al,* 'Quality, Non-Clinical and Clinical Considerations for Biosimilar Monoclonal Antibody Development: EU, WHO, USA, Canada, and BRICS-TM Regulatory Guidelines'

Rahalkar, *et al,* 'Quality, Non-Clinical and Clinical Considerations for Biosimilar Monoclonal Antibody Development: EU, WHO, USA, Canada, and BRICS-TM Regulatory Guidelines' (2018) 9 Frontiers in pharmacology 1079.

Rawson SB, 'Canada’s Adverse Drug Reaction Reporting System: A Failing Grade'

Rawson SB, 'Canada’s Adverse Drug Reaction Reporting System: A Failing Grade' (2015) 22(2) Journal of Population Therapeutics and Clinical Pharmacology

Reed, *et al*, 'Confidentiality, Privacy, and Respect: Experiences of Female Sex Workers Participating in HIV Research in Andhra Pradesh, India'

Reed, *et al*, 'Confidentiality, Privacy, and Respect: Experiences of Female Sex Workers Participating in HIV Research in Andhra Pradesh, India' (2014) 9(1) Journal of Empirical Research on Human Research Ethics 19

Reich and Bery, 'Expanding Global access to ARVs: The Challenges of Prices and Patents'

Reich and Bery, 'Expanding Global access to ARVs: The Challenges of Prices and Patents' (2005) The AIDS pandemic: Impact on science and society 324

Reinhardt, 'Adjudication without Enforcement in GATT Disputes'

Reinhardt, 'Adjudication without Enforcement in GATT Disputes' (2001b) 45(2) J Conflict Resolut 174

Rigamonti, 'The South Africa AIDS Controversy: A Case Study in Patent Law and Policy'

Rigamonti, 'The South Africa AIDS Controversy: A Case Study in Patent Law and Policy' (2005)

Roffe, Pedro and Vivas-Eugui, 'A Shift in Intellectual Property Policy in US FTAs?'

Roffe, Pedro and Vivas-Eugui, 'A Shift in Intellectual Property Policy in US FTAs?' (2007) 11(5) Bridges 15

Rubinstein*, et al*, 'The NIH Genetic Testing Registry: A new, Centralized Database of Genetic Tests to enable Access to Comprehensive Information and improve Transparency'

Rubinstein*, et al*, 'The NIH Genetic Testing Registry: A new, Centralized Database of Genetic Tests to enable Access to Comprehensive Information and improve Transparency' (2012) 41(1) Nucleic Acids Res D925

Sabi and Rieker, 'The role of Civil Society in Health Policy making in South Africa: a Review of the Strategies Adopted by the Treatment Action Campaign'

Sabi and Rieker, 'The role of Civil Society in Health Policy making in South Africa: a Review of the Strategies Adopted by the Treatment Action Campaign' (2017) 16(1) African Journal of AIDS Research 57

Sarkies, *et al,* 'Data Collection Methods in Health Services Research'

Sarkies, *et al,* 'Data Collection Methods in Health Services Research' (2015) 6(01) Applied clinical informatics 96

Shadlen, 'Patents and Pills, Power and Procedure: The North-South Politics of Public Health in the WTO'

Shadlen, 'Patents and Pills, Power and Procedure: The North-South Politics of Public Health in the WTO' (2004) 39(3) Stud Comp Int Dev 76

Sharp, Paul and Hahn, 'The Evolution of HIV-1 and the Origin of AIDS'

Sharp, Paul and Hahn, 'The Evolution of HIV-1 and the Origin of AIDS' (2010) 365(1552) Philosophical Transactions of the Royal Society B: Biological Sciences 2487

Simelela, *et al*, 'A Political and Social history of HIV in South Africa'

Simelela, *et al*, 'A Political and Social history of HIV in South Africa' (2015) 12(2) Current HIV/AIDS Reports 256

Smallman-Raynor, Matthew R and Andrew D, 'Civil War and the Spread of AIDS in Central Africa'

Smallman-Raynor, Matthew R and Andrew D, 'Civil War and the Spread of AIDS in Central Africa' (1991) 107(1) Epidemiology & Infection 69

Tarr E and Amalio T, 'Toxicogenetics of Antiretroviral Therapy: Genetic Factors that Contribute to Metabolic Complications'

Tarr E and Amalio T, 'Toxicogenetics of Antiretroviral Therapy: Genetic Factors that Contribute to Metabolic Complications' (2007) 12(7) Antivir Ther (Lond) 999

Tata B, Melvin A and Michael S, 'Barriers to Implementing Clinical Pharmacogenetics Testing in Sub-Saharan Africa. A Critical Review'

Tata B, Melvin A and Michael S, 'Barriers to Implementing Clinical Pharmacogenetics Testing in Sub-Saharan Africa. A Critical Review' (2020) 12(9) Pharmaceutics

Unit, Intellectual Property Rights, 'Poverty, Health & Intellectual Property Rights with Special Reference to India'

Unit, Intellectual Property Rights, 'Poverty, Health & Intellectual Property Rights with Special Reference to India' (2007) 126 Indian J Med Res 390

Vignali, *et al*, 'How Regulatory T cells Work'

Vignali, *et al*, 'How Regulatory T cells Work' (2008) 8(7) Nature reviews Immunology 523.

Walthall, Arron, 'Legal Pressure to Incorporate Pharmacogenetics in the UK'

Walthall, Arron, 'Legal Pressure to Incorporate Pharmacogenetics in the UK' (2005) 46 Jurimetrics 263.

Warnich, et al, ‘Pharmacogenomic Research in South Africa: Lessons Learned and Future Opportunities in the Rainbow Nation’

Warnich L, Drögemöller BI, Pepper MS, Dandara C, Wright GE. Pharmacogenomic Research in South Africa: Lessons Learned and Future Opportunities in the Rainbow Nation. Curr Pharmacogenomics Person Med. 2011 Sep;9(3):191-207. doi: 10.2174/187569211796957575. PMID: 22563365; PMCID: PMC3228231.

Waters, Elizabeth and Jodie Doyle, 'Systematic reviews of public health in developing countries are in train'

Waters, Elizabeth and Jodie Doyle, 'Systematic reviews of public health in developing countries are in train' (2004) 328(7439) BMJ 585

Wohlgemut JP, ‘AIDS, Africa and Indifference: A Confession’

Wohlgemut JP, ‘AIDS, Africa and Indifference: A Confession’ (2002) 167(5) CMAJ 485-487

Yang Q and others, ‘Estimates of the Number of Prevalent and Incident Human Immunodeficiency Virus (HIV) Infections in Canada, 2008’

Yang Q and others, ‘Estimates of the Number of Prevalent and Incident Human Immunodeficiency Virus (HIV) Infections in Canada, 2008’ (2010) 101(6) Canadian Journal of Public Health 486-490

Zakrison Tanya and Hamel Paul, ‘Access to Medicines - The Global Debate Over Free Trade’

Zakrison Tanya and Hamel Paul, ‘Access to Medicines - The Global Debate Over Free Trade’ (2001) University of Toronto Medical Journal

Zhou, *et Al,* ‘Emerging Role of Pharmacogenomics in HIV Research in Africa’

Zhou, *et Al,* ‘Emerging Role of Pharmacogenomics in HIV Research in Africa’ (2021) 16(5) Future Virology’

8.3 Case law

Association for Molecular Pathology v Myriad Genetics, Inc 569 U.S. 576

Bernstein and Others v Bester NO and Others 1996 (CCT23/95)

Carmichele v Minister of Safety and Security 2001 (4) SA 938 (CC)

Hoffmann v South African Airways 2001 1 SA 1 (CC)

Khoza v Member of the Executive Council for Health and Social Development of the Gauteng Provincial Government 2015 (3) SA 266 (GJ)

Kiyutin v Russia 2011 (2700/10)

Minister of Health v Treatment Action Campaign 2002 (5) SA 721 (CC)

N v MEC for Health, Gauteng (44761/2013)

NM v Smith (Freedom of Expression Institute as Amicus Curiae) 2007 (5) SA 250 (CC)

Sidaway v Bethlem Royal Hospital Governors & Others 1985 AC 871

Soobramoney v Minister of Health (Kwazulu-Natal) 1998 (1) SA 765 (CC)

Treatment Action Campaign v Minister of Health 2002(4) BCLR 356 (T)

Tshabalala-Msimang and Another v Makhanya and Others 2008 (6) SA 102 (W)

8.4 Legislation

Children's Act 35 of 2005

Constitution of the Republic of South Africa, 1996

Copyright Act 98 of 1978

Designs Act 195 of 1993

Health Professions Act 56 of 1974

Intellectual Property Laws Amendment Act 38 of 1997

Medicines and Related Substances Act 101 of 1965

Medicines and Related Substance Control Amendment Act 90 of 1997

Merchandise Marks Act 17 of 1941

National Health Act 61 of 2003

Parliament of South Africa Passed the Academy of Science of South Africa Act 67 of 2001

Patents Act 57 of 1978

Plant Breeders' Rights Act 15 of 1976

Promotion of Equality and Prevention of Unfair Discrimination Act 4 of 2000

Protection of Personal Information Act 4 2013

Public Finance Management Act 1 of 1999

Trademarks Act 194 of 1993

8.5 Legislation elsewhere

Data Protection Act 2018 c.12

Food and Drug Regulations (C.R.C., c. 870)

Food and Drugs Act (R.S.C., 1985, c. F-27)

General Data Protection Regulation (EU) 2016/679

Health Authorities Act 1995, c.17

Medicines Act of 1968,c.67

Ministry of Health Act 1919, c 2.1

Public Health Act 1961, c.64

8.6 Internet sources

Yu-Fan Wen and Thapi Matsaneng, 'Patents, Pharmaceuticals and Competition: Benefitting from an effective patent examination system' (CompCom 2014) https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Y+Wen+and+T+Matsaneng+%2C+%E2%80%98Patents%2C+Pharmaceuticals+and+Competition%3A+Benefitting+from+an+effe accessed 31 July 2019 .

Academy of Science of South Africa, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications'

Academy of Science of South Africa, 'Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications' (ASSAF 2018) http://dx.doi.org/10.17159/assaf.2018/0033 accessed 03 December 2021.

Adam Wagstaff and Mariam Claeson, 'The Millennium Development Goals for Health Rising to the Challenge'

Adam Wagstaff and Mariam Claeson, 'The Millennium Development Goals for Health Rising to the Challenge' (World Bank 2004.) https://openknowledge.worldbank.org/handle/10986/14954 accessed 07 December 2022

Alcom K 'Prep Impant Could last Well Over a Year'

Alcom K 'Prep Impant Could last Well Over a Year' (AidsMap 24 July 2019) https://www.aidsmap.com/bulletin/conference-news/ias-2019/24-july-2019 accessed 01 September 2019

All Things Considered' (12 January 1998)

'All Things Considered' (12 January 1998) http://www.npr.org/templates/story/story.php?storyId=1036870 accessed 30 September 2021.

'Annotated Agenda'

'Annotated Agenda' (UNAIDS 26 September 2018) https://www.unaids.org/sites/default/files/media_asset/20181211_UNAIDS_PCB43_Agenda_EN.pdf.

accessed 17 March 2019.

Anup Shah, ‘The World Trade Organization and Free Trade’

Anup Shah, ‘The World Trade Organization and Free Trade’ (WTO 02 July 2007)
https://www.wto.org/english/res_e/publications_e/ai17_e/trips_art27_jur.pdf
accessed 24 June 2019.

Ashleigh Furlong, ‘HIV treatment programme doing well but long way to go’

Ashleigh Furlong, ‘HIV treatment programme doing well but long way to go’ (GroundUp 26 June 2018)
https://www.groundup.org.za/article/hiv-treatment-programme-doing-well-long-way-go/
accessed 02 June 2019.

ASSAf, ‘Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications’

ASSAf, ‘Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications’ (Department of Science and Technology, 2018)
https://research.assaf.org.za/handle/20.500.11911/106
accessed 08 December 2022.

Bentley D, ‘The Human Genome Project—An Overview’ (2000) 20(3) Medicinal Research Reviews

Bentley D, ‘The Human Genome Project—An Overview’ (2000) 20(3) Medicinal Research Reviews
https://doi.org/10.1002/(SICI)1098-1128(200005)20:3<189::AID-MED2> 3.0.CO;2-%23
accessed 14 October 2021

Butler A, South Africa’s HIV/AIDS policy, 1994-2004: How can it be explained?

African Affairs, Volume 104, Issue 417, October 2005, Pages 591-614,
https://doi.org/10.1093/afraf/adi036 accessed 09 June 2023

The African Commission on Human and People's Rights, ‘56 Resolution on the Situation of Human Rights Defenders in Tunisia - ACHPR/Res.56(XXIX)01’ (07 May 2001

https://www.achpr.org/sessions/resolutions?id=61

07 December 2022.

Berger J and Prabhala A, ‘Assessing the Impact Of Trips-Plus Patent Rules in the Proposed US-Sacu Free Trade Agreement’

Berger J and Prabhala A, ‘Assessing the Impact Of Trips-Plus Patent Rules in the Proposed US-Sacu Free Trade Agreement’ https://www.who.int/hiv/amds/capacity/tza2_oxfamreport_pricing_financing.pdf accessed 07 October 2021.

Burch B, ‘Intrinsic and Extrinsic Factors in Drug Development’

Burch B, ‘Intrinsic and Extrinsic Factors in Drug Development’ (Nuventra 13 March 2019) https://www.nuventra.com/resources/blog/intrinsic-and-extrinsic-factors/ accessed 29 October 2020

Burgess L, Differences between HIV-1 and HIV-2’

Burgess L, Differences between HIV-1 and HIV-2’ (MedicalNews 5 December 2018) https://www.medicalnewstoday.com/articles/323893 accessed 10 October 2019.

Cameron E, ‘The fundamental barriers to access to medicine remain when they don’t need to’

Cameron E, ‘The fundamental barriers to access to medicine remain when they don’t need to’ (Daily Maverick 24 October 2018) https://www.dailymaverick.co.za/article/2018-10-24-the-fundamental-barriers-o-access-to-medicine-remain-when-they-dont-need-to/ accessed 16 September 2019

Carey G ‘HGSS: Human Genetics for the Social Science’

Carey G ‘HGSS: Human Genetics for the Social Science’ (16 January 2001) http://psych.colorado.edu/~carey/hgss/ accessed 20 April 2020.

CDC, ‘Pneumocystis pneumonia—Los Angeles’

CDC, ‘Pneumocystis pneumonia—Los Angeles’ (MMWR, 1981) https://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm

accessed 07 December 2022.

Chacko TK, ‘Trade Related Aspects of Intellectual Property Rights (TRIPS)’

Chacko TK, ‘Trade Related Aspects of Intellectual Property Rights (TRIPS)’ (New Delhi 16 November 2010)
http://wtocentre.iift.ac.in/FAQ/english/TRIPS.pdf
accessed 25 June 2019.

‘Columbia Mailman School of Public Health, ‘What is epidemiology?’

‘Columbia Mailman School of Public Health, ‘What is epidemiology?’ (Public Health 21 October 2020).
https://www.publichealth.columbia.edu/public-health-now/news/what-epidemiology
accessed 17 September 2021

Campion DP and FJ Dowell, ‘Translating Pharmacogenetics and Pharmacogenomics to the Clinic: Progress in Human and Veterinary Medicine’

Campion DP and FJ Dowell, ‘Translating Pharmacogenetics and Pharmacogenomics to the Clinic: Progress in Human and Veterinary Medicine’ (Front Vet Sci 11 February 2019)
https://doi.org/10.3389/fvets.2019.00022
accessed 03 December 2021.

Competition Commission Newsletter, 'Commission Questions Conduct of Anti-retroviral Companies No. 13'

Competition Commission Newsletter, 'Commission Questions Conduct of Anti-retroviral Companies No. 13' (CompCom 2003)
http://www.compcom.co.za/wp-content/uploads/2014/09/Dec-03-Newsletter.pdf
accessed 31 July 2019

‘Compulsory Licensing Request' (CPTech 07 March 2001)

‘Compulsory Licensing Request' (CPTech 07 March 2001)
http://www.cptech.org/ip/health/sa/ciplanetsh03072001.html
accessed 31 July 2019

Convention on Biological Diversity ‘IX/12.Access and benefit-sharing’

Convention on Biological Diversity ‘IX/12.Access and benefit-sharing’
https://www.cbd.int/decision/cop/?id=11655
accessed 06 December 2022.

Correa C, ‘Implications of the Doha Declaration on the TRIPS Agreements And Public Health’
Correa C, ‘Implications of the Doha Declaration on the TRIPS Agreements and Public Health’ (World Health Organization June 2002)
https://www.who.int/medicines/areas/policy/WHO_EDM_PAR_2002.3.pdf
accessed 01 September 2019.

Department of Trade and Industry, ‘Intellectual Property Policy’
Department of Trade and Industry, ‘Intellectual Property Policy’ (Phase 1, 2018)’
https://www.gov.za/sites/default/files/gcis_document/201808/ippolicy2018-phasei.pdf
accessed 07 October 2021

Donald G and McNeil JT, ‘South Africa's Bitter Pill for World's Drug Makers’
Donald G and McNeil JT, ‘South Africa's Bitter Pill for World's Drug Makers’ (The New York Times March 29, 1998)
https://www.nytimes.com/1998/03/29/business/south-africa-s-bitter-pill-for-world-s-drug-makers.html
accessed 30 September 2019

Dylan Mohan Gray, ‘Fire in the Blood’
Dylan Mohan Gray, ‘Fire in the Blood’ (YouTube March 2017)
http://www.youtube.com
accessed 19 May 2019

Fidler D, Correa CM and Aginam O, ‘Legal review of the General Agreement on Trade in Services (GATS) from a Health Policy Perspective’
Fidler D, Correa CM and Aginam O, ‘Legal review of the General Agreement on Trade in Services (GATS) from a Health Policy Perspective’ (World Health Organization, January 2006)
https://www.researchgate.net/publication/238743323_Legal_Review_of_the_G

eneral Agreement onTrade in Services GATS from a Health Policy Perspective
accessed 24 June 2019.

Flemming A, Chain B and Florey HW, 'The global resource for scientific evidence in animal Research'
Flemming A, Chain B and Florey HW, 'The global resource for scientific evidence in animal Research' https://www.sciencehistory.org/historical-profile/howard-walter-florey-and-ernst
accessed 28 April 2019

Frederick, 'WTO TRIPS Agreement and its Implications for Access to Medicines in Developing Countries'
Frederick, 'WTO TRIPS Agreement and its Implications for Access to Medicines in Developing Countries' (SSRN 09 September 2011)
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1924420
accessed 25 September 2019

Furlong A, 'HIV treatment programme doing well but long way to go'
Furlong A, 'HIV treatment programme doing well but long way to go' (GroundUp 26 June 2018) https://www.groundup.org.za/article/hiv-treatment-programme-doing-well-long-way-go/
accessed 02 June 2019

GATS, 'Agreement on National Treatment' (Article XVII)'
GATS, 'Agreement on National Treatment' (Article XVII)'
https://www.wto.org/english/res_e/publications_e/ai17_e/gats_art17_jur.pdf
accessed 09 July 2019.

General Assembly 'United Nations Millenium Declaration Resolution'
General Assembly 'United Nations Millenium Declaration Resolution' (United Nations 18 September 2000)
https://www.un.org/en/development/desa/population/migration/generalassembly/docs/globalcompact/A_RES_55_2.pdf
accessed 01 September 2019

Gey G, ‘Timeline of medical biotechnology’

Gey G, Timeline of Medical Biotechnology
https://www.biotechnology.amgen.com/timeline.html
accessed 18 May 2019.

Gilroy SA, ‘HIV Infection and AIDS’

Gilroy SA, ‘HIV Infection and AIDS’ (Medscape 08 October 2019)
https://emedicine.medscape.com/article/211316-overview
accessed 05 January 2020.

Global Fund, ‘HIV drug resistance report. 2017. CDC WHO - World Heal Organ’

Global Fund, ‘HIV drug resistance report. 2017. CDC WHO - World Heal Organ’ (2017)
https://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf
accessed 25 November 2019

Goldstein J, ‘Police Agencies Are Assembling Records of DNA’

Goldstein J, ‘Police Agencies Are Assembling Records of DNA’ (New York Times 12 June 2013) https://www.nytimes.com/2013/06/13/us/police-agencies-are-assembling-records-of-dna.html
accessed15 September 2020.

Goodman CG, ‘HTA 101: Introduction to Health Technology Assessment’

Goodman CG, ‘HTA 101: Introduction to Health Technology Assessment’ (Bethesda MD: National Library of Medicine (US) 2014)
https://www.nlm.nih.gov/nichsr/hta101/HTA_101_FINAL_7-23-14.pdf
accessed 07 December 2022

Gould L, ‘Practical pharmacovigilance analysis strategies’

Gould L, ‘Practical pharmacovigilance analysis strategies’ (01 November 2002) https://doi.org/10.1002/pds.771
accessed 04 October 2021

Government of Canada, ‘Adverse Reaction Information’

Government of Canada, ‘Adverse Reaction Information’ https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-information.html accessed 29 November 2022.

Government of Canada, ‘Canada’s Progress Towards Global HIV Targets (90-90-90)’

Government of Canada, ‘Canada’s Progress Towards Global HIV Targets (90-90-90)’ (2020) https://www.canada.ca/en/public-health/services/publications/diseases-conditions/canada-progress-towards-global-hiv-targets-90-90-90-2020.html accessed 28 November 2022

Government of Canada, ‘Summary: Estimates of HIV incidence, prevalence and proportion undiagnosed in Canada’

Government of Canada, ‘Summary: Estimates of HIV incidence, prevalence and proportion undiagnosed in Canada’ (2014) https://www.canada.ca/en/public-health/services/publications/diseases-conditions/summary-estimates-hiv-incidence-prevalence-proportion-undiagnosed-canada-2014.html accessed 22 November 2022

Hannah Keppler, ‘The Untold AIDS Story: How Access to Antiretroviral Drugs was Obstructed in Africa’

Hannah Keppler, ‘The Untold AIDS Story: How Access to Antiretroviral Drugs was Obstructed in Africa’ (The EJBM Blog 01 October 2013) https://theejbm.wordpress.com/2013/10/01/the-untold-aids-story-how-access-to-antiretroviral-drugs-was-obstructed-in-africa/ accessed 05 April 2019

Hawkins BR, ‘Economic Constitutionalism and Policy Space in Complex Systems of Multi-Level Governance: The Case of Trade and Health’

Hawkins BR, ‘Economic Constitutionalism and Policy Space in Complex Systems of Multi-Level Governance: The Case of Trade and Health’ (University

of York, 15 July 2018) https://pure.york.ac.uk/portal/en/publications/economic-constitutionalism-and- policy-space-in-complex-systems-of
accessed 07 December 2022

'Health Policy Project'
'Health Policy Project' https://www.healthpolicyproject.com/index.cfm?id=topics-Stigma
accessed 30 October 2020

'Healthcare Data Breach Statistics'
'Healthcare Data Breach Statistics' (HIPAA Journal, December 2021) https://www.hipaajournal.com/healthcare-data-breach-statistics/
accessed 2 August 2022.

'HIV Drug Resistance: A New Threat for Low- and Middle-Income Countries'
'HIV Drug Resistance: A New Threat for Low- and Middle-Income Countries' (Avert News 06 Jan 2017) https://www.avert.org/news/hiv-drug-resistance-new-threat-low-and-middle-income-countries
accessed 28 November 2019

HIV Genotyping Laboratory
HIV Genotyping Laboratory (Witwatersrand University) https://www.wits.ac.za/pathology/divisions/molecular-medicine--haematology/research-and-analytical-services/hiv--haematology-molecular-diagnostics-unit/hiv-genotyping/
accessed 17 January 2019

HM Government
HM Government https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/920378/Genome_UK_-_the_future_of_healthcare.pdf
accessed 1 December 2022

http://capping.slis.ualberta.ca/global/sandra/history.html
accessed 30 January 2019

http://content.time.com/time/arts/article/0,8599,43510,00.html
accessed 19 September 2018

http://indexmedicus.afro.who.int/iah/fulltext/incidencepdf.pdf
accessed 30 October 2019

http://librarypdf.catie.ca/PDF/ATI-40000s/40264.pdf
accessed 13 September 2019

http://www.achpr.org/files/instruments/women-protocol/achpr_instr_proto_women_eng.pdf
accessed 03 December 2021

http://www.africa-union.org/root/au/AboutAu/Constitutive_Act_en.htm
accessed 03 December 2021

http://www.aidsmap.com/resources/treatmentsdirectory/drugs/Zidovudine-AZT-iRetroviri/page/1730919/
accessed 22 October 2018

http://www.dailymaverick.co.za
accessed 21 September 2018

http://www.dnaftb.org/1/bio.html
accessed 22 October 2018

http://www.globalissues.org/article/42/the-wto-and-free-trade#ChinasEntryintotheWTO
accessed 24 June 2019

http://www.health.gov.za/
accessed 22 October 2018.

http://www.i-based.info/htb-south/314
accessed on 01 September 2019

http://www.lateralmag.com/columns/gene-dosage/pythagoras-the-fava-of-pharmacogenomic
accessed 10 October 2018

http://www.refworld.org/docid/453882a422.html
accessed 02 December 2021

http://www.section27.org.za/content/uploads/2010/10/TauvGSKevidenceAndLegalSubmissions.pdf accessed 31 July 2019

http://www.statssa.gov.za
accessed 13 March 2019

http://www.ubuntu.thiyagaraaj.com/Home/about-ubuntu/ubuntu-philosophy-meaning
accessed 05 September 2020

http://www.virusmyth.com/aids/hiv/abazt2.htm
accessed 22 October 2018

http://www.who.int/news-room/fact-sheets/detail/hiv-aids
accessed 10 October 2018

http://www.who.int/reproductivehealth/ghs-strategies/en/
accessed 20 September 2018

http://www.wollheim-memorial.de/en/entstehung_der_deutschen_farbenindustrie
accessed 28 May 2019

https://academic.oup.com/biostatistics/pages/About
accessed 15 January 2022

https://admespipp.blogspot.com/2015/12/un-pulse-dag-hammarskjold-library.html
accessed 01 September 2019

https://aidsinfo.nih.gov/guidelines
accessed on 13 September 2018

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/31/adverse-effects-of-antiretroviral-agents
accessed 17 October 2017

https://archive.org/stream/bookbulletin3740sanf/bookbulletin3740sanf_djvu.txt
accessed 22 October 2018

https://assaf.org.za/index.php/news/520-assaf-launches-study-on-human-genetics-and-genomics-2
accessed 28 October 2020

https://au.int/en/treaties/african-charter-rights-and-welfare-child
accessed 03 December 2021

https://blog.talent360.co.za/general/south-african-health-products-regulatory-authority-sahpra/
accessed 26 November 2020

https://clarkstonconsulting.com/insights/personalized-medicine-2019/
accessed 30 October 2020

https://courses.lumenlearning.com/boundless-business/chapter/international-trade-agreements-and-organizations/
accessed 09 July 2019

https://definitions.uslegal.com/t/trips-agreement/
accessed 30 July 2019

https://digitallibrary.un.org/record/705437?ln=en
accessed 01 September 2019

https://emea.illumina.com/science/technology/next-generation-sequencing.html
accessed 15 September 2020

https://ffarmo.com/big-pharma/

accessed 17 June 2020

https://genomicmedicineuk.com/?s=ADME&lang=en
accessed 29 October 2020

https://ghr.nlm.nih.gov/primer/genomicresearch/snp
accessed 19 October 2018

https://ghr.nlm.nih.gov/primer/testing/sequencing
accessed 25 April 2020

https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines
accessed 6 January 2022

https://hivskeptic.wordpress.com/tag/pride-chigwedere
accessed 22 October 2018

https://koersjournal.org.za/index.php/koers/article/download/757/870/0
accessed 23 March 2021

https://medicaldictionary.thefreedictionary.com/polymorphic+genetic+marker
accessed 17 January 2019

https://obamawhitehouse.archives.gov/precision-medicine
accessed 21 March 2020

https://ophs@berkeley.edu
accessed 25 November 2020

https://pandomics.com/access
accessed 16 April 2020

https://patent.laws.com/patent-law-history
accessed 10 May 2019

https://pharmaphorum.com/sales-marketing/are-dual-arvs-the-new-frontier-in-a-maturin
accessed 18 October 2018

https://report.nih.gov/
accessed 22 October 2018

https://stackoverflow.com/questions/1291942/what-does-javascriptvoid0-mean
accessed 12 September 2019

https://study.com/academy/lesson/genotyping-phenotyping-definitions-processes-uses.html
accessed 22 October 2018

https://web.stanford.edu/group/journal/cgi-bin/wordpress/wp-content/uploads/2012/09/Siddiqi_SocSci_2005.pdf
accessed 30 July 2019

https://www.ands.org.au/working-with-data/sensitive-data/medical-and-health
accessed 08 April 2020

https://www.atlasantibodies.com/resources/human-protein-atlas/blood-atlas/
accessed 10 April 2020

https://www.avert.org/about-hiv-aids/cure#:~:text=There%20is%20no%20cure%20for,some%20residual%20virus%20may%20remain accessed 13 October 2019

https://www.cdc.gov/mmwr/preview/mmwrhtml/lmrk077.htm
accessed 21 October 2018

https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm340007.pdf accessed 19 September 2018

https://www.genome.gov
accessed 22 October 2018

https://www.gov.uk/government/publications/the-nhs-constitution-for-england/the-nhs-constitution-for-england#patients-and-the-public-your-responsibilities
accessed 28 November 2022

https://www.healthline.com/health/hiv-aids/antiretroviral-drugs-side-effects-adherence accessed 09 July 2018

https://www.history.com/topics/industrial-revolution/industrial-revolution
accessed 28 April 2019

https://www.hiv.gov/federal-response/pepfar-global-aids/pepfar
accessed 27 September 2018

https://www.livescience.com/37247-dna.html
accessed 17 October 2018

https://www.livescience.com/37247-dna.html
accessed 21 October 2019

https://www.mayoclinic.org/diseases-conditions/hiv-aids/symptoms-causes/syc-20373524
accessed 22 October 2018

https://www.msf.org/south-africa-country-takes-landmark-step-access-medicines
accessed 10 May 2019

https://www.nat.org.uk/about-hiv/hiv-statistics
accessed 30 October 2020

https://www.nature.com/scitable/definition/allele-48/
accessed 07 December 2022

https://www.ncbi.nlm.nih.gov/books/NBK2263/
accessed 22 October 2018

https://www.ncbi.nlm.nih.gov/pubmed/20235850
accessed 22 October 2018

https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development
accessed 22 October 2018

https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development
accessed 27 May 2019

https://www.poz.com/basics/hiv-basics/hiv-clinical-trials
accessed 12 October 2020

https://www.researchgate.net/publication/5362289_Economic_advantage_of_pharmacogenomics-Clinical-trials_with_genetic_information
accessed 05 March 2020

https://www.sahpra.org.za/press-releases/sahpra-launches-the-med-safety-app-for-self-reporting-of-suspected-adverse-drug-reactions-by-the-public-and-healthcare-professionals/
accessed 19 October 2022

https://www.sahpra.org.za/wp-content/uploads/2020/01/2.01_General-information_-Jul19_v10.pdf
accessed 20 September 2021

https://www.samrc.ac.za/innovation/genomics-centre
accessed 25 August 2022

https://www.thepharmaletter.com/article/special-report-personalized-medicine
accessed 16 October 2021

https://www.thepharmaletter.com/article/special-report-personalized-medicine
accessed 16 October 2021

https://www.trade.gov/free-trade-agreement-overview
accessed 6 October 2021

https://www.ucl.ac.uk/laws/people/sir-robin-jacob
accessed 18 May 2019

https://www.un.org/en/about-us/universal-declaration-of-human-rights
accessed 01 December 2021

https://www.un.org/millenniumgoals/2015_MDG_Report/pdf/MDG%202015%20rev%20(July%201).pdf accessed 15 September 2021

https://www.unicef.org/esaro/UNICEF_South_Africa_--_2017_--_Health_Budget_Brief.pdf accessed 03 December 2021

https://www.upcounsel.com/history-of-patents
accessed 28 April 2019

https://www.va.gov/vdl/documents/Clinical/Comp_Patient_Recrd_Sys_(CPRS)/cprssetup.pdf accessed 01 November 2020

https://www.who.int/teams/social-determinants-of-health/declaration-of-alma-ata
accessed 02 December 2021

https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring/ accessed 17 September 2021

https://www.wma.net/policies-post/wma-declaration-of-geneva/
accessed 07 December 2022

https://www.wto.org/english/res_e/booksp_e/gatt_ai_e/art20_e.pdf
accessed 17 July 2019

https://www.wto.org/english/res_e/booksp_e/gatt_ai_e/art20_e.pdf
accessed 30 January 2019

Katella K, ‘How HIV Became the Virus We Can Treat’

Katella K, ‘How HIV Became the Virus We Can Treat’ (Yale Medicine, 12 October 2021) https://www.yalemedicine.org/news/hiv-treatable accessed 07 December 2022

Leonard J, ‘How does antiretroviral therapy work?’

Leonard J, ‘How does antiretroviral therapy work?’ (Medical News Today 29 November 2020) https://www.medicalnewstoday.com/articles/324013 accessed17 September 2021

Lovgren S, ‘HIV originated with monkeys, not chimps, study finds’

Lovgren S, ‘HIV originated with monkeys, not chimps, study finds’ (National Geographic Science News, 12 June 2003) https://www.nationalgeographic.com/science/article/news-hiv-aids-monkeys-chimps-origin accessed 17 September 2021

McCall A and Quinn G, ‘The FDA process, patents and market exclusivity’

McCall A and Quinn G, ‘The FDA process, patents and market exclusivity’ (CPA Global Report 12 March 2017) https://msmgf.org/wpcontent/uploads/2015/09/Access_Challenges_for_HIV_treatment_KAPs.pdf accessed 13 September 2018

MHRA, ‘Guidance on adverse drug reactions’

MHRA, ‘Guidance on adverse drug reactions’ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949130/Guidance_on_adverse_drug_reactions.pdf accessed 1 December 2022

‘Most Favoured Nation and National Treatment’

‘Most Favoured Nation and National Treatment’ https://phdessay.com/most-favoured-nation-and-national-treatment/ accessed 23 September 2021

Mungadze S, ‘Life Healthcare Reveals Damage Caused by Data Breach’

Mungadze S, ‘Life Healthcare Reveals Damage Caused by Data Breach’ (IT Web, 31 August 2020) https://www.itweb.co.za/content/rW1xLv59YPGvRk6m accessed 2 August 2022

National Department of Trade and Industry, ‘Intellectual Property Policy’

National Department of Trade and Industry, ‘Intellectual Property Policy’ (Phase 1, 2018)’ https://www.gov.za/sites/default/files/gcis_document/201808/ippolicy2018-phasei.pdf accessed 07 October 2021

‘National Department of Trade and Industry: Directorate: Pharmaceuticals and Medical Devices’

‘National Department of Trade and Industry: Directorate: Pharmaceuticals and Medical Devices’ (28 June 2017) http://www.sapcconference.za.org/wp-content/uploads/2019/12/Gillian-Christians.pdf accessed 07 October 2021

National Institutes of Allergy and Infectious Diseases, ‘Antiretroviral Drug Discovery and Development’

National Institutes of Allergy and Infectious Diseases, ‘Antiretroviral Drug Discovery and Development’ (NIH 2018) https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development#:~:text=The%20pivotal%20ACTG%20019%20trial%20investigated%20whether%20it,first%20demonstration%20of%20a%20treatment%20for%20HIV%20infection accessed 15 September 2021.

National Research Council,

National Research Council, https://www.avert.org/professionals/hiv-social-issues/stigma-d accessed 08 November 2019

Ndlovu L, ‘South African Patent Law and Access to Medicine’

Ndlovu L, ‘South African Patent Law and Access to Medicine’ (Research Gate November 2013)

https://www.researchgate.net/publication/264236381_South_African_Patent_Law_and_Access_to_Medicines
accessed 30 July 2019

NHS Health Research Authority,
NHS Health Research Authority, https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/ accessed 1 December 2022

Park C Agrees, 'Limiting the Number of Licensees may Hinder the Robust Generic Competition that can Bring Prices Down'
Park C Agrees, 'Limiting the Number of Licensees may Hinder the Robust Generic Competition that can Bring Prices Down' (AIDS Map 26 July 2012) http://www.aidsmap.com/news/jul-2012/intellectual-property-still-threat-antiretroviral-access-says-panel
accessed 01 September 2019

Tucker C and Amalia R, 'Privacy Protection, Personalized Medicine and Genetic Testing'
Tucker C and Amalia R, 'Privacy Protection, Personalized Medicine and Genetic Testing' (09 July 2015) https://www.ftc.gov/system/files/documents/public_comments/2015/09/00010-97509.pdf
accessed 08 January 2022

Rai D 'Non-Discrimination Principle: MFN and National Treatment in the GATT'
Rai D 'Non-Discrimination Principle: MFN and National Treatment in the GATT' (IPleaders 1994) http://www.blog.ipleaders.in/non-discrimination-principle-most-favoured-nation-mfn-and-national-treatment-in-the-general-agreement-on-tariffs-and-trade-gatt-1994/
accessed 23 September 2021

Reddy M, 'The Economic And Socio-economic benefits of R&D-based Multinational pharmaceuticals on the South African economy'
Reddy M, 'The Economic And Socio-economic benefits of R&D-based Multinational pharmaceuticals on the South African economy' (Deloitte 2007)

http://ipasa.co.za/Downloads/IPASA%20and%20Pharmaceutical%20Industry%20Profile/Research%202007/IMSA%20Book%20071013.pdf
accessed 31 July 2019

Richey LA and Haakonsson SJ, 'Access to ATV Treatment: Aid, Trade and Governance in Uganda'

Richey LA and Haakonsson SJ, 'Access to ATV Treatment: Aid, Trade and Governance in Uganda' (2014)
https://www.files.ethz.ch/isn/18786/Access_ARV_Treatment.pdf
accessed 02 August 2019

Rosenberg J, 'Risk of Heart Failure Doubled in People Living with HIV, Contagion Live'

Rosenberg J, 'Risk of Heart Failure Doubled in People Living with HIV, Contagion Live' (Infectious Diseases today 08 January 2019)
https://www.contagionlive.com/news/risk-of-heart-failure-doubled-in-people-
accessed 25 November 2019

Russell S, 'New Crusade to Lower AIDS Drug Costs'

Russell S, 'New Crusade to Lower AIDS Drug Costs' (The San Francisco Chronicle 24 May 1999) https://www.sfgate.com/health/article/New-Crusade-To-Lower-AIDS-Drug-Costs-Africa-s-2929307.php
accessed 30 September 2019

SAHPRA, 'Pharmacovigilance systems'

SAHPRA, 'Pharmacovigilance systems' (May 2022)
https://www.sahpra.org.za/wp-content/uploads/2022/05/SAHPGL-CEM-PV-02_Pharmacovigilance-Systems_Version-1.0.pdf
accessed 28 October 2022

SAHPRA, 'Promotion of Access to Information Act (PAIA) manual'

SAHPRA, 'Promotion of Access to Information Act (PAIA) manual'
https://www.sahpra.org.za/document/paia-manual/
accessed 20 November 2022

Saloman L, 'TAF vs. TDF: Measuring Lipid Levels in HIV Treatment'

Saloman L, ‘TAF vs. TDF: Measuring Lipid Levels in HIV Treatment’ (Contagion Live 21 November 2019) https://www.contagionlive.com/view/taf-vs-tdf-measuring-lipid-levels-in-hiv-treatment accessed 04 September 2019

Shah observes that the reality is far from the principle. Anup Shah, ‘The World Trade Organization and Free Trade’

Shah observes that the reality is far from the principle. Anup Shah, ‘The World Trade Organization and Free Trade’ (WTO 02 July 2007) https://www.wto.org/english/res_e/publications_e/ai17_e/trips_art27_jur.pdf accessed 24 June 2019

South African Department of Health, ‘National Drug Policy for South Africa’

South African Department of Health, ‘National Drug Policy for South Africa’ (1996) https://www.gov.za/documents/national-drugs-policy accessed 16 September 2019

South African Health Products Regulatory Authority, ‘Guidelines for Adverse Drug Reaction ADR’s Reporting for Health Care Professionals’

South African Health Products Regulatory Authority, ‘Guidelines for Adverse Drug Reaction ADR’s Reporting for Health Care Professionals’ (28 March 2022) https://www.sahpra.org.za/wp-content/uploads/2020/04/ADR-Reporting-Guideline_HCPs_v1_for-commenting_March-2020.pdf accessed 07 December 2022

South African National AIDS Council, ‘South African National LBGTI HIV framework’

South African National AIDS Council, ‘South African National LBGTI HIV framework’ (2017) https://www.gov.za/sites/default/files/gcis_document/201705/nsp-hiv-tb-stia.pdf accessed 04 November 2019

Staff Reporter, ‘Blood Cell Transcriptome Atlas Enables Study of Immune Disorder’

Staff Reporter, ‘Blood Cell Transcriptome Atlas Enables Study of Immune Disorder’ (Genome Web19 December 2019)

https://www.genomeweb.com/sequencing/blood-cell-transcriptome-atlas-enables-study-immune-disorders#.YV6zntpBzIU
accessed 10 April 2020

Stein L, 'Record number of HIV cases reported in Saskatchewan'
Stein L, 'Record number of HIV cases reported in Saskatchewan' (CJME, 1 June 2022) https://www.cjme.com/2022/06/01/record-number-of-hiv-cases-reported-in-saskatchewan-not-done/
accessed 28 November 2022

Stemple L, 'Health and human rights in today's fight against HIV/AIDS'
Stemple L, 'Health and human rights in today's fight against HIV/AIDS' https://doi.org/10.1097/01.aids.0000327443.43785.a1
accessed 6 October 2022

Steven Benowitz, 'Looking across genomic medicine's gaps and opportunities'
Steven Benowitz, 'Looking across genomic medicine's gaps and opportunities' (06 July 2016)
https://www.genome.gov/news/news-release/GM8-Looking-across-genomic-medicines-gaps-and-opportunities
accessed 21 August 2022

UN Sustainable Development Goals Report
UN Sustainable Development Goals Report (2022)
https://unstats.un.org/sdgs/report/2022/The-Sustainable-Development-Goals-Report-2022.pdf
accessed 22 November 2022

Technology Advice for Small Businesses, 'EHRs vs paper records: Which is better?'
Technology Advice for Small Businesses, 'EHRs vs paper records: Which is better?' (TechAdvisory 04 February 2019)
https://www.techadvisory.org/2019/02/ehrs-vs-paper-records-which-is-better/
accessed 12 October 2019

The Lancet

The Lancet (Lancet Editorial, 06 January 2018)
https://www.sciencedirect.com/journal/the-lancet/vol/391/issue/10115
accessed 06 December 2022

'The South Africa dossier on the Consumer Project on Technology internet pages'
'The South Africa dossier on the Consumer Project on Technology internet pages' http://www.cptech.org/ip/health/sa/
accessed 23 September 2021.

'The South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022'
'The South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022' https://www.gov.za/sites/default/files/gcis_document/201705/nsp-hiv-tb-stia.pdf
accessed 17 March 2019

Torjesen I, 'One-size-fits-all' approach will not work for drug evaluation and funding'
Torjesen I, 'One-size-fits-all' approach will not work for drug evaluation and funding' (The Pharmaceutical Journal, 26 APR 2016) https://pharmaceutical-journal.com/article/news/one-size-fits-all-approach-will-not-work-for-drug-evaluation-and-funding
accessed 26 November 2020

Tucker C and Amalia R, 'Privacy Protection, Personalized Medicine and Genetic Testing'
Tucker C and Amalia R, 'Privacy Protection, Personalized Medicine and Genetic Testing' (09 July 2015)
https://www.ftc.gov/system/files/documents/public_comments/2015/09/00010-97509.pdf
accessed 08 January 2022

UK Research and Innovation
UK Research and Innovation, https://www.ukri.org/about-us/mrc/our-policies-and-standards/research/data-management-and-sharing/
accessed 1 December 2022

UNAIDS 'Global HIV & AIDS statistics — Fact sheet'

UNAIDS ‘Global HIV & AIDS statistics — Fact sheet’
https://www.unaids.org/en/resources/fact-sheet
accessed 11 October 2022

‘UNAIDS Calls for Greater Urgency as Global Gains Slow and Countries Show Mixed Results Towads 2020 HIV Target’
‘UNAIDS Calls for Greater Urgency as Global Gains Slow and Countries Show Mixed Results Towads 2020 HIV Target’ (UNAIDS 16 July 2019) https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2019/july/20190716_PR_UNAIDS_global_report_2019 accessed 13 October 2019

‘The Under 30 Using Genomic Data To Find Cures And Save Billions’
‘The Under 30 Using Genomic Data To Find Cures And Save Billions’ (Forbes 15 Feb 2017) https://www.forbes.com/video/5254637751001/using-genomic-data-to-find-cures-and-save-billions/?sh=39bdb52f1750
accessed 15 September 2019

UNICEF, ‘Health Budget South Africa’
UNICEF, ‘Health Budget South Africa’
https://www.unicef.org/esa/sites/unicef.org.esa/files/2018-09/UNICEF-South-Africa-2017-Health-Budget-Brief.pdf
accessed 08 January 2021

UNITAID ‘The Medicines Patent Pool and AbbVie sign licensing agreement to increase access to crucial HIV treatments throughout Africa’
UNITAID ‘The Medicines Patent Pool and AbbVie sign licensing agreement to increase access to crucial HIV treatments throughout Africa’ (UnitAid 10 December 2015) https://unitaid.org/news-blog/medicines-patent-pool-abbvie-sign-licensing-agreement-increase-access-crucial-hiv-treatments-throughout-africa/#en
accessed 6 October 2021

‘UnitAID Medicines Patent Pool’

‘UnitAID Medicines Patent Pool’ (UnitAID 13 July 2015) https://unitaid.org/news-blog/unitaid-medicines-patent-pool-publish-hiv-drug-patent-survey/#en accessed 31 July 2019

'Universal Declaration on the Human Genome and Human Rights’

'Universal Declaration on the Human Genome and Human Rights’ (11 November 1997) https://en.unesco.org/themes/ethics-science-and-technology/human-genome-and-human-rights accessed 23 November 2022

William W, Fisher II and Rigamonti CP, ‘The South Africa AIDS Controversy A case Study in Patent Law and Policy’

William W, Fisher II and Rigamonti CP, ‘The South Africa AIDS Controversy A case Study in Patent Law and Policy’ (Harvard Law School 10 February 2005) https://cyber.harvard.edu/people/tfisher/South%20Africa.pdf accessed 07 December 2022

WIPO ‘Paris Convention’

WIPO ‘Paris Convention’ https://www.wipo.int/treaties/en/ip/paris/ accessed 6 October 2021

World Health Organization ‘Human rights and health’.

World Health Organization ‘Human rights and health’ (WHO 29 December 2017) https://www.who.int/news-room/fact-sheets/detail/human-rights-and-health accessed 17 July 2019

World Health Organization ‘Recommendations on the Diagnosis of HIV Infection in Infants and Children’

World Health Organization ‘Recommendations on the Diagnosis of HIV Infection in Infants and Children’ (World Health Organization May 2010) https://www.ncbi.nlm.nih.gov/books/NBK138552/ accessed 25 October 2020

World Health Organization, ‘Report on Trade, Foreign Policy, Diplomacy and Health’

World Health Organization, ‘Report on Trade, Foreign Policy, Diplomacy and Health’ https://www.who.int/trade/trade_and_health/en/
accessed 19 July 2019

World Health Organization, ‘HIV Policy Adoption and Implementation Status in Countries’

World Health Organization, ‘HIV Policy Adoption and Implementation Status in Countries’ (July 2019) https://apps.who.int/iris/bitstream/handle/10665/326035/WHO-CDS-HIV-19.20-eng.pdf?ua=1
accessed 28 November 2019

World Health Organization, ‘Millennium Development Goals’

World Health Organization, ‘Millennium Development Goals’ (Goal 6, Target 2 B)’ (WHO 19 February 2018) https://www.who.int/news-room/fact-sheets/detail/millennium-development-goals-(mdgs)
accessed 01 September 2019

World Health Organization, ‘WHO’s Science Council Launches Report calling for Equitable Expansion of Genomics’

World Health Organization, ‘WHO’s Science Council Launches Report calling for Equitable Expansion of Genomics’ (12 July 2022) https://www.who.int/news/item/12-07-2022-who-s-science-council-launches-report-calling-for-equitable-expansion-of-genomics
accessed 07 December 2022

World Trade Organisation, ‘Staff Working Paper ERSD-2018-01’

World Trade Organisation, ‘Staff Working Paper ERSD-2018-01’ (22 February 2018) https://www.wto.org/english/res_e/reser_e/ersd201801_e.pdf
accessed 30 August 2022

World Trade Organization ‘Article XXI Security Exceptions’

World Trade Organization ‘Article XXI Security Exceptions’ (WTO 01 January 2016) https://www.wto.org/english/res_e/booksp_e/gatt_ai_e/art21_e.pdf
accessed 09 July 2019

World Trade Organization Report.,' Supporting access to treatment in developing countries across the world'

World Trade Organization Report.,' Supporting access to treatment in developing countries across the world' (WTO 18 July 2012, updated 30 April 2018) https://www.wto.org/english/res_e/publications_e/world_trade_report18_e.pdf accessed 15 June 2019

World Trade Organization.' 'Declaration on the TRIPS agreement and public health'

World Trade Organization.' 'Declaration on the TRIPS agreement and public health' (WHO 14 November 2001 https://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm accessed 06 September 2021

Yethi D, 'Shortage of ARVs spark infection fears'

Yethi D, 'Shortage of ARVs spark infection fears' (The Star 5 June 2019) https://www.pressreader.com/south-africa/the-star-south-africa-late-edition/20190605/281522227582607 accessed 26 May 2019

Young R, 'Impact of Data Management on Clinical Trials: New Study'

Young R, 'Impact of Data Management on Clinical Trials: New Study' (Pharmaphorum 18 December 2017) https://pharmaphorum.com/r-d/views-analysis-r-d/impact-data-management-clinical-trials-new-study/ accessed 10 October 2019

Annexure 1: UNISA CLAW ethical clearance

UNISA university of south africa

UNISA CLAW ETHICS REVIEW COMMITTEE

Date 20180216

Reference: PS of 2018
Applicant: AP Molusi

Dear Adv Molusi

Decision: ETHICS APPROVAL
FROM 16 FEBRUARY 2018
TO 15 FEBRUARY 2021

Researcher(s): Angela Patricia Molusi

Supervisor (s): Prof MN Labuschaigne

Ethical and legal issues relating to pharmacogenetics and the development of personalized medicine in the field of HIV

Qualification: R & D

Thank you for the application for research ethics clearance by the Unisa CLAW Ethics Review Committee for the above mentioned research. Ethics approval is granted for 3 years.

*The **negligible risk application** was reviewed by the CLAW Ethics Review Committee on 16 February 2018 in compliance with the Unisa Policy on Research Ethics and the Standard Operating Procedure on Research Ethics Risk Assessment. The decision was ratified by the committee.*

The proposed research may now commence with the provisions that:

1. The researcher will ensure that the research project adheres to the values and principles expressed in the UNISA Policy on Research Ethics.
2. Any adverse circumstance arising in the undertaking of the research project that is relevant to the ethicality of the study should be communicated in writing to the CLAW Committee.
3. The researcher will conduct the study according to the methods and procedures set out in the approved application.

University of South Africa
Preller Street, Muckleneuk Ridge, City of Tshwane
PO Box 392 UNISA 0003 South Africa
Telephone: +27 12 429 3111 Facsimile: +27 12 429 4150
www.unisa.ac.za

4. Any changes that can affect the study-related risks for the research participants, particularly in terms of assurances made with regards to the protection of participants' privacy and the confidentiality of the data, should be reported to the Committee in writing, accompanied by a progress report.
5. The researcher will ensure that the research project adheres to any applicable national legislation, professional codes of conduct, institutional guidelines and scientific standards relevant to the specific field of study. Adherence to the following South African legislation is important, if applicable: Protection of Personal Information Act, no 4 of 2013; Children's act no 38 of 2005 and the National Health Act, no 61 of 2003.
6. Only de-identified research data may be used for secondary research purposes in future on condition that the research objectives are similar to those of the original research. Secondary use of identifiable human research data require additional ethics clearance.
7. No field work activities may continue after the expiry date of 15 February 2021. Submission of a completed research ethics progress report will constitute an application for renewal of Ethics Research Committee approval.

Note:
The reference number P5 of 2018 should be clearly indicated on all forms of communication with the intended research participants, as well as with the Committee.

Yours sincerely,

PROF D GOVENDER

Chair of CLAW ERC

E-mail: govend1@unisa.ac.za

Tel: (012) 429-9482

PROF OS SIBANDA

Executive Dean: CLAW

E-mail: sibanos@unisa.ac.za

Tel: (012) 429-8374

University of South Africa
Preller Street, Muckleneuk Ridge, City of Tshwane
PO Box 392 UNISA 0003 South Africa
Telephone: +27 12 429 3111 Facsimile: +27 12 429 4150
www.unisa.ac.za

Annexure 2: Turnitin digital receipt

turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Angela Patricia Molusi
Assignment title:	Revision 1
Submission title:	MEDICO-LEGAL ISSUES RELATING TO PHARMACOGENOMICS ...
File name:	Chapter_1_to_7__12_December_2022_1_2_AP_Final_draft.docx
File size:	491.12K
Page count:	267
Word count:	63,207
Character count:	365,918
Submission date:	13-Dec-2022 01:22PM (UTC+0200)
Submission ID:	1980112460

Annexure 3: Turnitin summary report

MEDICO-LEGAL ISSUES RELATING TO PHARMACOGENOMICS AND THE DEVELOPMENT OF PERSONALISED MEDICINE IN THE CONTEXT OF HIV AND AIDS IN SOUTH AFRICA

ORIGINALITY REPORT

25%	16%	20%	10%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	hdl.handle.net Internet Source	3%
2	www.pulp.up.ac.za Internet Source	1%
3	upetd.up.ac.za Internet Source	1%
4	"Encyclopedia of AIDS", Springer Science and Business Media LLC, 2018 Publication	1%
5	Marietjie Botes, Melodie Nöthling Slabbert, Antonel Olckers. "Data Commercialisation in the South African Health Care Context", Potchefstroom Electronic Law Journal, 2021 Publication	1%
6	repository.up.ac.za Internet Source	1%
7	uir.unisa.ac.za Internet Source	1%