Self-Reported Antenatal Medicines Use Among Women Living with and Without HIV in Western Cape, South Africa: A Sub-Analysis of the B Positive Cohort Study

By

Zaineb ELzouki (ELZZAI001)

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Supervisor: Dr. Ushma Mehta
Co-supervisor: Prof. Marc Blockman

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DECLARATION

I**, Zaineb Elzouki**, hereby declare that the work on this dissertation/ thesis is based is my original work (except where acknowledgements indicate otherwise) and that the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Globally, innumerable women take medication while they are pregnant, and this trend is growing. The pipeline of medicines targeting maternal comorbidities is expanding. However, for most medicines, there is insufficient data on their safety in pregnancy. In addition, women may be taking medication for chronic or acute conditions before they recognize that they are pregnant.

This study compared the self-reported pattern of medicine use during the course of pregnancy in a cohort of pregnant women either living with or without HIV; seeking care at Gugulethu primary health care obstetric clinic in Western Cape, South Africa. Data on medicine use was collected over 3 antenatal visits. Medications reported were manually classified and coded by a clinical pharmacist and medical doctor.

Structured interviews using a detailed questionnaire on medication use were administered to n=989 pregnant women. Women who had an ectopic pregnancy or an elective termination of pregnancy (TOP) were excluded from the analysis. 982 of these women were included in our analysis (n=507 HIV-negative and n=475 HIV-positive). Of these, 39 (4.0%) did not report taking any medicine during pregnancy. Most 907 (92.3%) pregnant women reported using at least one over-the-counter medicine (OTC) and the majority, 601 (61.2%), at least one prescription medicine. A total of 36 (3.7%) reported using at least one herbal or traditional medicine over the course of the pregnancy.

Pregnant women living with HIV were significantly less likely to report use of OTC medicine (56.2% vs 77.7%, p=<0.001). Pregnant women living with HIV also reported less herbal medicine use (2.9% vs 4.7%, p=0.07) compared to pregnant women living without HIV, though the effect was non-significant within this sample.

Excluding antiretroviral medicines, prescription medicine use was essentially the same among pregnant women living with and without HIV (30.5% vs 30.2%, p=0.96). Exposure to medicines known to be potentially teratogenic or unsafe in pregnancy was reported in 300 (30.65%) pregnant women, with aspirin 238 (24.2%) and non-steroidal anti-inflammatory medicines 46 (4.7%) medicines being the most reported.

This study provides valuable information on self-reported medication use among pregnant women living with and without HIV in a South African primary healthcare setting. Medicine use was widespread in the study cohort, particularly OTC, with high prevalence of potentially unsafe medicines used during pregnancy. Our finding highlights the urgent need to build awareness around rational and safe medicine use among antenatal staff; pharmacists; and women of child-bearing age in South Africa, encouraging the taking of a thorough history of medicine exposure throughout the antenatal period.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ANC	Antenatal clinics
ART	Antiretroviral Treatment
ATC	Anatomical Therapeutic Chemical
EMA	European Medicines Agency
FDA	Food and Drug Administration
FHS	Faculty of Health Sciences
GA	Gestational age
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
MOU	Midwife Obstetric Unit
NSAIDs	Non-Steroidal Anti-Inflammatory drugs
OTC	Over-the-Counter
PI	Product information
PM	Prescribed Medication
PrEP	Pre-exposure prophylaxis
PWLO HIV	Pregnant women live without HIV
PWLW HIV	Pregnant women living with HIV
TB	Tuberculosis
TGA	Therapeutic Goods Administration
THMs	Traditional and Herbal Medicines
TOP	Termination of pregnancy
T1	First trimester
T2	Second trimester
T3	Third trimester
UCT	University of Cape Town

CHAPTER 1: INTRODUCTION

1.1 Background

The thalidomide tragedy that occurred in the late 1960s, when the drug was prescribed for the management of morning sickness in pregnant women, resulted in the birth of approximately 10,000 babies with severe birth defects, and an unknown number of miscarriages and stillbirths. This historic event highlighted the falsity of the assumption that the placenta is an impenetrable barrier and that the fetus was relatively protected from exposure to medicines used by pregnant women. It also highlighted the importance of exercising caution in the use of medicines during pregnancy and the need for careful studies examining their effect on the fetus [1]. More broadly, the thalidomide catastrophe highlighted the need for the regulation of medicines in terms of their safety, as well as efficacy, before they are licensed for use. This medical disaster has also been credited as a major event that sparked the creation of international efforts to systematically monitor the safety of medicines once they have been licensed [2]. It highlighted the limitation of preclinical studies, including animal studies, as well as pre-marketing clinical trials in understanding the safety profile of a medicine. It also reinforced the fact that medicines can, and do, cross the placenta, and that their effects upon the developing fetus are far from understood [3]. The systematic exclusion, from clinical trials, of specific subpopulations who may be particularly at risk of harm, such as pregnant women, continues to be a standard of practice, perpetuating the limited knowledge of the safety performance of these medicines in these populations at the time of licensing. Preclinical animal studies remain the primary source to assess toxicity and potential teratogenic risk before licensing. However, due to significant anatomical and

physiological disparities between the different mammalian species, animal studies often do not reliably predict the risk a particular compound may pose to the human fetus [4].

Women of child-bearing age may take medication for chronic or acute conditions before they recognize that they are pregnant, resulting in unintentional early exposure to medicines during the pregnancy. Women may self-medicate or seek care for the early symptoms of pregnancy, such as morning sickness, frequent urination and fatigue. As the pregnancy evolves, medical conditions, such as gestational diabetes, gestational hypertension, urinary tract infection, and lower back pain may further require therapeutic interventions. Moreover, pregnant women may self-medicate for minor ailments such as heartburn, colds and flus, and body aches and pains. As a result of these medical issues, pregnant women will be exposed to prescription or self-administered medicines.

Pregnant women are a challenging population to treat, since the health of both the mother and her unborn child need to be considered in therapeutic decision-making. In some instances, these treatments are employed to intentionally treat fetal conditions. Steroids, for example, might be administered to the mother to encourage fetal lung growth for the benefit of the fetus. In other instances, the optimal management of the mother's medical condition/s may protect the fetus from adverse outcomes consequent to the underlying condition. However, in some situations, medications used in pregnancy may harmfully affect fetal development and growth [5].

A key aspect of safe and rational prescribing in pregnancy is understanding the teratogenic potential of medicines [6]. The teratogenic potential of a medicine depends on a host of factors, including: [6]

a) The innate biological capacity of the medicine to harm fetal tissue (often identified in animal studies)
b) The presence of genetic factors that may increase the fetus's susceptibility
c) The extent to which the medicine crosses the placenta (pharmacokinetic profile)
d) The dose and duration of treatment at which a teratogenic effect becomes likely
e) The period of exposure during the pregnancy

Pregnancy is a precise and complex process that includes various phases. Each organ of the fetus develops at a specific time called the *critical period*. During these critical periods, the fetus becomes particularly sensitive to any harm caused by a medication, or by any other teratogen. For that reason, some medications can be unsafe for use within the first trimester but safe in the second or third trimester [7]. For example, valproic acid exposure in the early first trimester can lead to major malformations, such as neural tube defect, cleft lip, and cleft palate. Prolonged exposure, later in pregnancy, can lead to behavioral and cognitive impairment, which is only seen later in childhood, manifesting as memory difficulties, decreased general intelligence, speech and language learning difficulties, and autism [8].

Recently, there is an increasing awareness of the need to exercise caution with the use of medicines during pregnancy, while ensuring that women are not denied

access to potentially life-saving treatments because of inadequate and imprecise information on the safety of such therapies in pregnancy. The American Food and Drug Administration (FDA) and European Medicines Agency (EMA) have also recently revised their guidelines on labelling for pregnancy and lactation [9,10]. This is seen as an optimistic effort to simply and accurately instruct healthcare experts and patients of the possible threats that a medicine may pose when utilized during pregnancy, without creating undue concern. In addition, these labelling changes also provide reassurance to both the prescriber and woman when no risks, or only limited risks, have been identified. Ensuring that information on the safety of medications during pregnancy and lactation is easily available to both pregnant women and their care providers will improve medicine prescribing in this group, while supporting a shared decision-making approach between carer and patient [11].

Improving the survival and health of mothers and newborns is a global priority. As a middle-income country, South Africa is home to many who are plagued by challenges of limited access to medical care, poor living conditions, and maternal malnutrition, all of which are likely to contribute to poor maternal health and pregnancy outcomes [12]. Moreover, maternal and neonatal health is significantly compromised by the high prevalence of HIV, with an estimated 7.9 million people living with HIV [13]. The antenatal prevalence of HIV in South Africa has been reported at approximately 30% in 2017 [14]. Confidential enquiries into maternal deaths have consistently highlighted the significant role of HIV disease in maternal morbidity and mortality. In 2003 South Africa launched its antiretroviral (ARV) program at public health facilities, and in 2015 there were significant improvements in guidelines to make every effort to ensure that all pregnant and breastfeeding

women who are living with HIV have access to ARV at antenatal clinics [15]. The introduction of ARVs has had a transformative impact on the reduction of HIV transmission from mothers to infants, while also greatly improving the health of women [16].

1.2 Rationale for the Research

Assessing the extent and patterns of medicine use during pregnancy through observational studies can provide important information on the common conditions that require treatment during this period, treatment-seeking behaviour, risk of exposure to potential teratogens or unsafe medicines and predisposing factors for potentially unsafe medicine use during pregnancy. This can inform initiatives aimed at supporting the rational and safe use of medicines by highlighting the importance of building health literacy and agency in decision-making around the use of medicines among women of child-bearing potential, pregnant women, and their health care providers.

Few studies exploring the patterns of medicine use in pregnancy have been conducted in South Africa. The report by Aviv, which was published 10 years before the rollout of antiretrovirals, found that approximately 71.2% of women interviewed around the time of delivery self-reported medication use during the course of their pregnancy. Disconcertingly only 31% of the women reported receiving advice regarding the use of medications during pregnancy [17].

Some studies reported only on the prevalence of use of one specific traditional medicine, like the report by Varga and Veale, who examined the utilization of

isihlambezo, a commonly used traditional medicine, and the effects of its use in pregnancy [18]. Kooi and Theobald reported on the knowledge and beliefs of using a traditional medicine named *Kgaba* among pregnant women, traditional healers, and midwives [19]. Other researchers, like De Wet and Ngubane, reported on the use of plants for gynaecological and obstetric conditions [20]. Most of these studies have been small and uncontrolled, and none have assessed how HIV infection influences medicine use in pregnancy.

Given the high prevalence of HIV among pregnant women in South Africa, it is important to understand and compare rates and patterns of medicine use among HIV-uninfected and HIV-infected women. By virtue of the need for chronic ART, the importance of adherence to treatment and the risk of drug interactions associated with ART, engagement with medicines is likely to be significantly different between pregnant women living without HIV (PWLO HIV) and pregnant women living with HIV (PWLW HIV). However, it is unclear whether patterns of other (non-antiretroviral) medicines use differs between these populations.

Therefore, this study aims to describe and compare the self-reported pattern of medicine use during the course of pregnancy in a cohort of pregnant women living with and without HIV.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Studies exploring the use of medication in pregnancy can be valuable in identifying the health seeking behaviour of pregnant women and recognizing health challenges facing them and their babies. These studies can support the future development to improve quality of medicine practise and develop policies to limit harmful medicines use in pregnancy, especially in developing countries.

Medication use during pregnancy may vary according to the geographical area, and this limits our ability to rely on data derived from different socioeconomic contexts and settings. Estimates of medicine use derived from studies assessing the nature and extent of medicine use in pregnancy are extremely variable. Among these studies, estimations were high in high income countries such as France (90%), Germany (85%), Japan (69%) and New Zealand (67%) [21-24].

Developing countries, especially in Africa, have limited access to health care, a paucity of qualified health professionals, and a lack of public awareness on the safety of medication use. Regulatory frameworks and enforcement mechanisms are weak, with uncontrolled access to prescribed medication (PM), over-the-counter medicine (OTC), and traditional herbal medicines (THM).

Developing and developed countries also differ in the profile of diseases that affect women of child-bearing age. HIV, TB, and malaria affect women in Africa to a much greater extent than their counterparts in Europe, America, and Asia [25]. The impact of these factors on the nature and extent of medication used in pregnancy is a vital

area for exploration, particularly since the use of medicines in pregnancy requires special considerations.

Therefore, the aim of this literature review is to gain a better understanding of the extent and pattern of medicines used by pregnant women in Africa. The review will explore how medication use in pregnancy has been studied in Africa; the extent to which medication use in pregnancy has evolved over the years, particularly in the African setting, while exploring differences in patterns of medicines used in pregnancy in different African settings. The review will also identify and report on literature on exposures to potentially harmful medicines and their timing of exposure during the pregnancy.

2.2 Method of Literature Review

This study conducted a review on the use of medicines (including prescription, OTC, and THM) in pregnant African women. The review focused on the type of medicines used and the extent to which they were used in African settings.

2.2.1 Databases Searched

The relevant publications included in this literature review were searched in following databases: PubMed; ScienceDirect; UpToDate; ResearchGate; EMBASE; Cochrane Library; UCT Library; Google scholar and Science Direct.

2.2.2 Search Methods Used

The database search was conducted online via the University of Cape Town (UCT) Health Sciences Library platform by the MPhil candidate. The search was limited to

human studies in Africa published in English during time the period 1993–2020. Identified articles were listed and downloaded if available. For any full text articles not available, the individual journals were searched or the corresponding authors of those manuscripts were contacted. Seven articles could not be sourced. Books, theses, and conference proceeding and abstracts were excluded from the search.

2.2.3 Search Terms

The search for the articles with the subject of interest was performed starting from January 2021, by mentioning all the names of African countries, including the variants in Anglophone, Francophone, Lusophone, and Arabophobe. The key terms used in the search were: “drug used in pregnancy” OR “prescribed medication in pregnancy” OR “self-reporting medication use in pregnancy” OR “Maternal consumption of over the counter or herbal medication” OR “herbal and traditional medicine use in Africa” OR “African countries”.

2.2.4 Eligibility Criteria

Studies were included if they:

1) Were published in English

2) Involved primary research

3) Were conducted in the African continent

4) Covered the topic of interest

5) Assessed the use of a specific or all categories of medicines e.g. PM, OTC, or THM during pregnancy

Studies were excluded if they:

1) Assessed illicit drug use in pregnancy

2) Confined their assessment to a single therapeutic category or specific medication e.g. antiretrovirals alone as these were more cantered around adherence and impact on disease and birth outcomes.

2.2.5 Data Extraction

A data extraction tool was applied to extract the key information from the selected studies. Data extracted included: title, author, journal, year of publication, Period of study, geographic location of the study, number of participants, type of enrolment facility, research question/aim, study design, percentage of pregnant women who used medication, type of medication used e.g. prescribed or self-medication and most commonly used medicines. The standardized data extraction and eligibility evaluation were performed by the MPhil student.

2.3 Results

2.3.1 Included Articles

The initial electronic search elicited (N=61) articles for review, of which (n=37) articles fulfilled the eligibility criteria and were included in the literature review. Twenty four articles were excluded, as they were either not a primary study (n=9), or did not fulfil the eligibility criteria (n=8), or there were no text articles available (n=7), as shown in the flow chart. The included articles were analyzed by grouping them according to the country in which the research was performed (**Figure 2.1**), year of publication and type of pharmaceuticals. Twenty (37%) African countries out of a total of 54 African countries were represented in the studies included in this review.

Although our search was restricted to English language, 11 articles from the non-English speaking countries were included. Some countries had more than one published article on this topic, such as Nigeria (n=7), Ethiopia (n=6), Ghana (n=3), Zimbabwe, Egypt, Uganda, Kenya and Sierra Leone (n=2 each). There were no papers that covered more than one country.

Figure 2.1 Articles Included in Systematic Review According to their Geographical Region

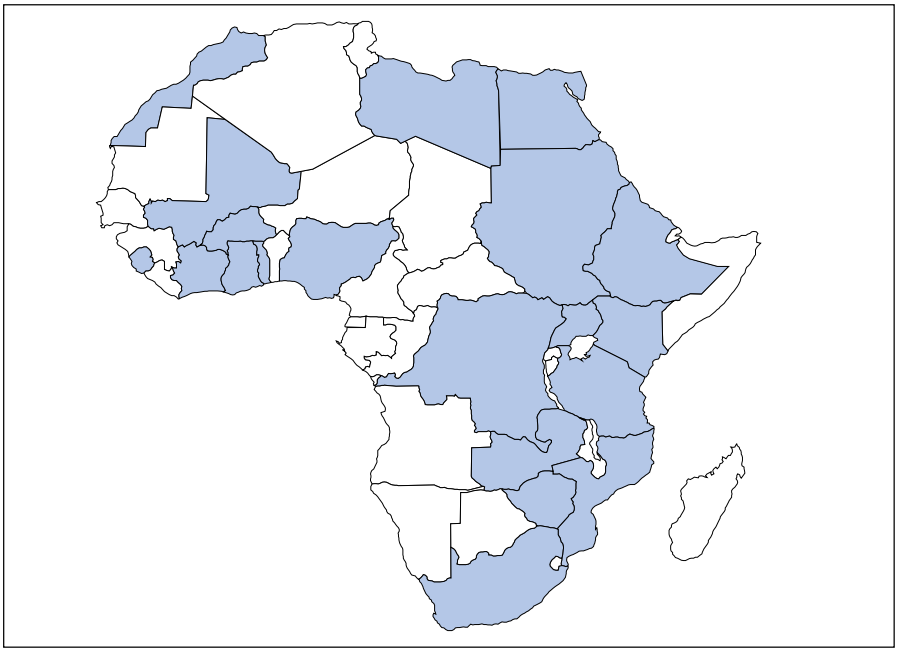


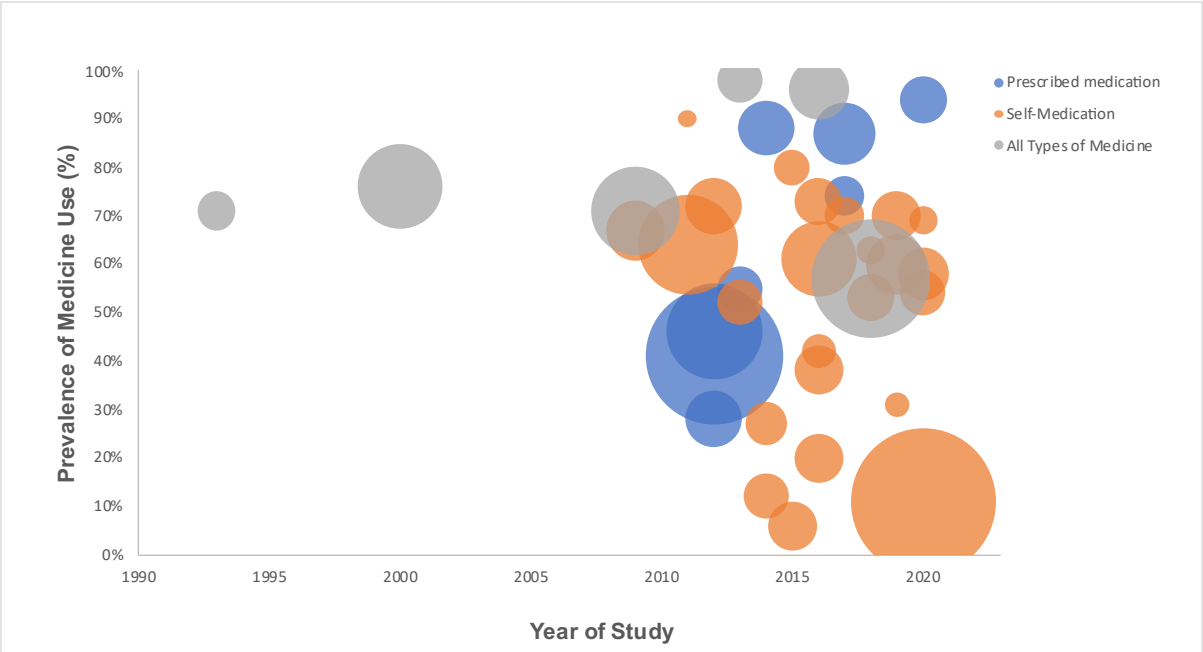
Figure 2.1 African countries highlighted in blue represent the geographical region of included articles

2.3.2 Study Characteristics

The bubble chart reflected in **Figure 2.2** depicts the reported prevalence of medication used by pregnant women in Africa per study over the last 30 years. The size of the bubble represents the study sample size and the colour denotes the type of medicine use investigated. A bubble's horizontal position notes the year of the study, and the vertical position notes the prevalence (reflected as a percentage of the total cohort) of medication used in each study. Two studies were excluded from the bubble chart because they did not provide a prevalence of medication use.

The graph demonstrates the increasing interest of research in this area of study as well as the increasing sample size of these studies in recent years. Most of the studies were conducted in the last decade with patterns of herbal medicine use attracting more attention from the scientific community. More than half of the studies show a high prevalence of medication use (>50%) particularly when all types of medicine use was investigated.

Figure 2.2 Prevalence of Medicines Use During Pregnancy Among Pregnant Women in Africa Per Year



Most of the studies, 32 (86.5%), were conducted in the last 10 years. The studies were mainly based in Sub-Saharan Africa, 32 (86.5%), and only five (13.5%) from North Africa. Seven studies (19%) were conducted only in urban settings, five (13.5%) were conducted in rural populations, and eight (21.6%) included women from both urban and rural settings. Unfortunately, many studies, 17 (46%), did not mention the type of community the cohort was derived from. The study size ranged between 100 and 3500 subjects. Medication histories were collected by questionnaire in 31 (83.8%) studies. The majority of studies focused on the use of herbal medicine (**Figure 2.3**).

Of all studies included, 13 (35%) took place in single health facilities. While 20 (54%) studies were conducted at multiple levels of health care facilities. The majority of the studies included, 25 (67.5%), took place at antenatal health services, with roughly four studies taking place in tertiary hospitals, two in secondary hospitals, and just two in a private hospital. Four did not mention the type of facility. None of the studies were conducted in a community setting **(Figure 2.4)**.

Figure 2.3 Types of Medicines Use Reported in the Included Studies

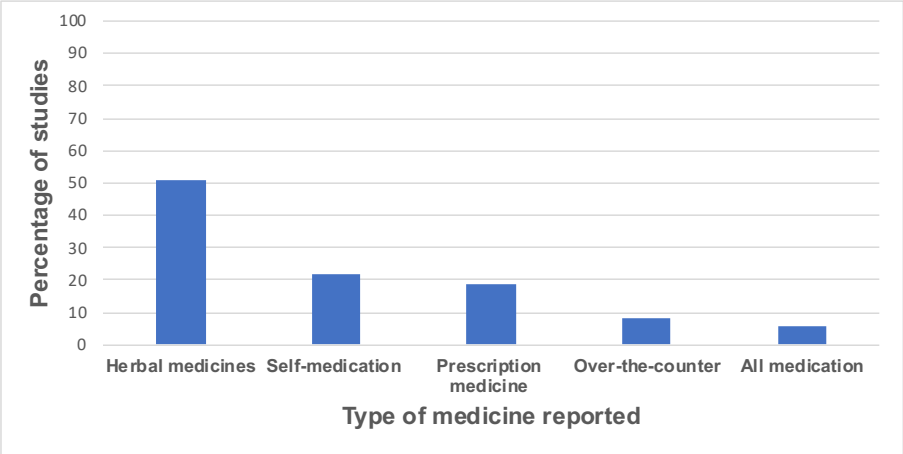


Figure 2.4 Number of Facilites Reported in Reviewed Studies

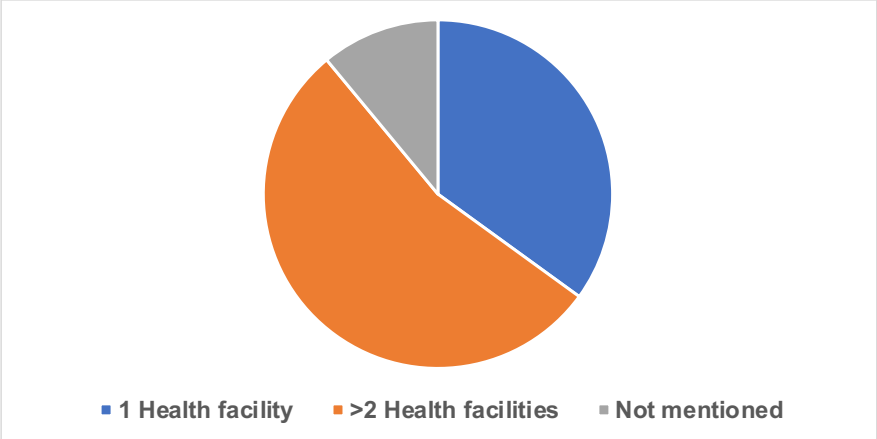


Table 2.1 Characteristics of Studies Included in the Literature Review

First Author (reference number)	Year of publication	Country of research	Sample size	Methodology/study design	Prevalence of medicine use
Gharoro *et al*. [26]	2000	Nigeria	1200 pregnant women	Cross sectional study	All medicine76% Herbal 12%
Fakeye *et al*. [27]	2009	Nigeria	595 pregnant women	Structured questionnaire	Herbal 67%
Yusuff *et al*. [28]	2011	Nigeria	1,650 pregnant women	Prospective cross sectional study	Self- medication 64% (58.4% used orthodox medicines 31.2% used local herbs 10.4% used both)
Abasiubong *et al* [29]	2012	Nigeria	518 pregnant women	Two-stage random sampling method	Prescribed 28% Self-medication 72%
Oshikoya *et al*. [30]	2012	Nigeria	1536 case files were analysed	Retrospective descriptive study	Prescribed 46% (excluding haematinics)
Abubakar *et al*. [31]	2014	Nigeria	3374 prescriptions	Retrospective study	No total percentage was reported
Obadeji *et al*. [32]	2020	Nigeria	369 pregnant women	Cross sectional survey	Prescribed 94% Self-medication 32%
Kebede *et al*. [33]	2009	Ethiopia	1268 pregnant women	Institution-based cross sectional study	All medicine 71%. Self-medication 12%(either over the counter or prescription drugs or traditional herbs)
Mohammed *et al*. [34]	2013	Ethiopia	339 pregnant women	Institution-based cross sectional study	Prescribed 55% OTC* 52% (excluding supplements)
Admasie *et al*. [35]	2014	Ethiopia	510 pregnant women	Institution-based cross sectional study	Prescribed 88%
Laelago *et al*. [36]	2016	Ethiopia	363 pregnant women	Institution-based cross sectional study	Herbal 73%
Molla *et al*. [37]	2017	Ethiopia	647 pregnant women	Institution-based cross sectional study	Prescribed 87%
Nega *et al*. [38]	2019	Ethiopia	600 pregnant women	Quantitative study	Herbal 60% Self-medication (Prescribed, OTC, excluding supplements) 42.5%

Adusi-Poku *et al*. [39]	2015	Ghana	384 pregnant women	Cross sectional study	Herbal 6%
Ameade *et al*. [40]	2018	Ghana	370 pregnant women	Cross sectional study	Herbal 53%
Gbagbo *et al*. [41]	2020	Ghana	136 pregnant women	Institution based cross sectional study	Self-medication 69%
Mawoza *et al*. [42]	2019	Zimbabwe	398 women either pregnant or had been pregnant and/or given birth before	Cross sectional study	Traditional medicine 70%
Dimene *et al*. [43]	2020	Zimbabwe	343 pregnant women or who had just given birth	Cross sectional study	Herbal 54%
Orief *et al*. [44]	2014	Egypt	300 pregnant women	Cross sectional study	Herbal 27%
Hanafy *et al*. [45]	2016	Egypt	600 pregnant women	Cross sectional study	All medicine 96% Prescribed 96% OTC 4% Herbal 42%
Kyegombe *et al.* [46]	2016	Uganda	400 pregnant women	A descriptive cross sectional study	Herbal 38%
Nyeko *et al*. [47]	2016	Uganda	383 postnatal mothers	A descriptive cross sectional study	Herbal 20%
James *et al*. [48]	2018	Sierra Leone	134 pregnant women	Cross sectional study	Herbal 63%
Mothupi. [49]	2014	Kenya	333 women who had delivered within the past 9 months	Cross sectional study	Herbal 12%
Kodhiambo. [50]	2017	Kenya	250 pregnant women	Cross sectional study	Prescribed 74% Self-medication 70%
Fukunaga. [51]	2020	Tanzania	3530 women who had a live born infant between 2014-2016 (data from population-based survey	representative, population-based survey	Herbal 11%

Malan *et al*. [52]	2011	Côte d'Ivoire	55 pregnant women	Ethnobotany survey	Herbal 90%
Rouamba *et al*. [53]	2018	Burkina Faso	2371 pregnant women	prospective observational cohort study	All medicine 57% (excluding sulphadoxine-pyrimethamine and iron-folic acid)
El khoudri *et al*. [54]	2016	Morocco	181 women who had delivered within the last 5 yrs.	A retrospective study	Herbal 42%
Khalf *et al*. [55]	2019	Libya	106 pregnant women	A descriptive cross sectional study	OTC 31%
Potchoo *et al*. [56]	2009	Togo	627 pregnant women	A retrospective study	No total percentage was reported
El Hajj *et al*. [57]	2020	Zambia	446 pregnant women	Cross sectional study	Herbal 58%
Nergard *et al*. [58]	2015	Mali	209 pregnant women	Quantitative, ethnobotanical interview study including a descriptive part	Herbal 80%
Sevene *et al*. [59]	2012	Mozambique	3105 pregnant women	Observational cohort study	Prescribed 41%
Haggaz *et al*. [60]	2013	Sudan	340 pregnant women	Cross sectional study	All medicine 98% Self-medication 3% Herbal 1%
Aviv *et al*. [17]	1993	South Africa	236 pregnant women	Cross sectional study	All medicine 71% Prescribed 59% Self-medication 29%
Mbarambara *et al*. [61]	2016	DR Congo	920 pregnant women	Cross sectional study	Self-medication 61%

Table 2.1 *OTC: over-the-counter medicine

2.3.3 Patterns of Medication Use by Pregnant Women in Africa

2.3.3.1 Prescribed Medication (PM)

a) Medicine Classification Systems: While most studies classified medication according to their therapeutic classes, such as antimalarial, antibiotics or antiemetics, eleven studies provided information about potential risk by applying the old FDA risks classification system (**Table 2.2**). One study used both FDA and Australian Therapeutic Goods Administration (TGA) classification [53]. One study classified medicine types according to the Anatomical Therapeutic Chemical (ATC) classification [30].

Vitamins and minerals were included with prescribed medication in most studies. Only three studies excluded vitamins and minerals or provided separate estimations [30,34,38,53].

Table 2.2 Prevalence of Pregnant Women Who Used Prescription Medication with Potential Risk of Fetal Harm According to the FDA Risk Classification

Author	Year	Country	Sample size	category D	category X	Reported teratogenic medicine
Oshikoya *et al*. [30]	2012	Nigeria	1536 case files were analysed	13%	0%	lorazepam, diazepam, acetylsalicylic acid, sulfadoxine/pyrimethamine, lisinopril, diclofenac
Abubakar *et al*. [31]	2014	Nigeria	3374 prescriptions	2.3%	0%	doxycycline
Obadeji *et al*. [32]	2020	Nigeria	369 pregnant women	0%	0%	-
Kebede *et al*. [33]	2009	Ethiopia	1268 pregnant women	3.3%	0.1%	hydroxyprogesterone, acetyl salicylic acid, phenobarbitone, propylthiouracil, warfarin, oestradiol valerate
Mohammed *et al.* [34]	2013	Ethiopia	339 pregnant women	16.8%	7.1%	atenolol, flouroquinolones, tetracycline, efavernez, valporoic acid, phenobarbitone, phenytoin, carbamazepine, warfarin
Admasie *et al*. [35]	2014	Ethiopia	510 pregnant women	5.3%	5.5%	quinine, co-trimoxazole
Molla *et al*. [37]	2017	Ethiopia	647 pregnant women	0.5%	0%	cotrimoxazole, diclofenac
Hanafy *et al*. [45]	2016	Egypt	600 pregnant women	0.5%	0.9%	ovulation-stimulating drugs, NSAIDs*
Kodhiambo. [50]	2017	Kenya	250 pregnant women	4.4%	0.4%	-
Rouamba *et al*. [53]	2018	Burkina Faso	2371 pregnant women	0.2%	-	cotrimoxazole
Sevene *et al*. [59]	2012	Mozambique	3105 pregnant women	16%	0%	kanamycin, doxycycline, tetracycline, captopril, povidone iodine

Table 2.2 * NSAIDs: Non-Steroidal Anti-Inflammatory drugs

b) Most Common PM Used: The proportion of women who were taking PM during pregnancy ranged from 28–96%. The most commonly prescribed medicines included haematinics, antimalarials, analgesics, and antibiotics.

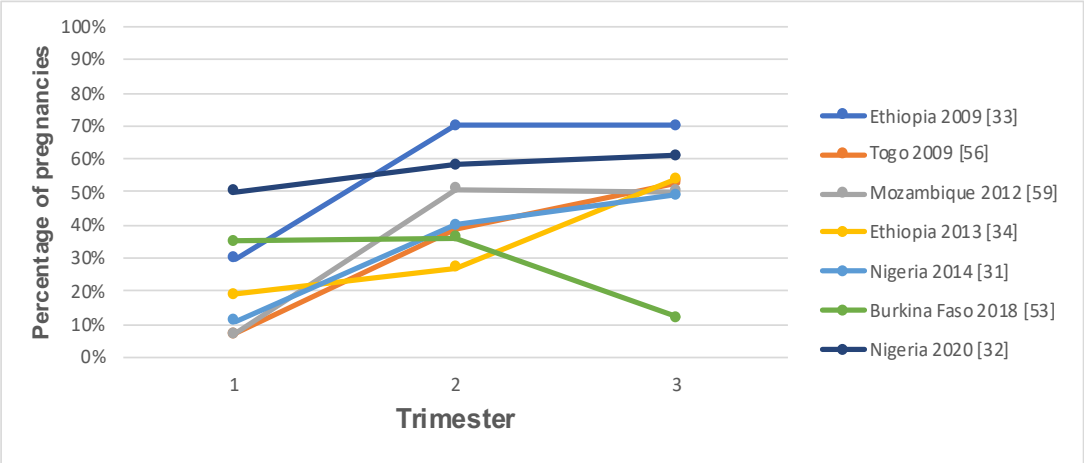
c) Availability of PM: Appropriate dispensing of PM during pregnancy supports rational medication use; so physicians and pharmacist should have updated knowledge with regarding the harmful effects of medicines used in pregnancy in order to advise and prescribe medication according to indication, correct dose and timing of exposure in relation to gestational age.

Kamuhabwa and colleagues assessed the knowledge of dispensing personnel in 200 pharmacies and found that only 38.8% of the pharmacies had a qualified pharmacist and more than half of the pharmacies were manned by pharmaceutical personnel who were not formally trained, including nurse assistants and sales persons [62]. Potchoo and colleagues reported that (88.5%) of prescriptions were written by midwives [56].

Health professionals should provide counselling and advice to pregnant women if they use medicines with or without prescription. Mohammed and colleagues, found that only 15% of pregnant women received advice at antenatal clinics (ANC), among whom only 18.3% received such counselling from pharmacists [34]. Aviv and colleagues, noted that only 31% of 236 pregnant women received advice regarding the use of medications during pregnancy [17]. Kodhiambo *et al.* reported that prescription-only medicines, such as amoxicillin, can be obtained from pharmacies without a prescription [50].

D) Use of PM Based on Stage of Pregnancy: Overall medication exposures based on the trimester of pregnancy were reported in only seven studies as demonstrated in **Figure 2.4**. These studies generally showed increases in PM use from the first to the third trimester of pregnancy. In contrast, Rouamba *et al.* reported a reverse trend of prescription behaviour, with a lower proportion of pregnant women reporting medication use in the third trimester compared to the first trimester [53]. Information about how the trimesters of pregnancy exposure was assessed was mentioned in only 2 studies. Potchoo *et al.* used the last menstrual period, month of pregnancy or expected date of delivery based on what was recorded in the women's medical file[56]. Rouamba *et al.* ascertained the trimester of medicines exposure by calculating the difference between the date of prescription or self- medication use and the reported date of the last menstrual period [53]. The rest of the studies did not give any information about how they ascertained the gestational timing of medication exposures.

Figure 2.5 Comparison of Studies Reporting Percentage of Women Prescribed Medication by Trimester



F) Factors Associated with PM Use During Pregnancy: Some studies assessed the association between various clinical, socioeconomic, and demographic factors and medication use during pregnancy. Maternal age had no effect on medication use in most studies while higher gravidity and urban areas of living were more likely to be associated with increased PM use (**Table 2.3**). Interestingly, in 3 studies primigravid women were *more* likely to receive prescription medicines, compared to multigravid women. However, co-morbidity, low education and hospitalisation were also predictors of high prescription use.

Table 2.3 Factors Associated with Prescribed Medication Use Among Pregnant Women

Author	Year	Country (Sample size)	Factors associated with high medicine use	Factors not found to be associated with high medicine use
Potchoo *et al*. [56]	2009	Togo (627)	Concurrent surgical condition	Age (14–45), parity, obstetric- gynaecological history
Sevene *et al*. [59]	2012	Mozambique (3105)	Primigravid, history of hospital admission	Age (mean age was 25 years)
Mohammed *et al*. [34]	2013	Ethiopia (339)	Rural residency, history of comorbidity or adverse pregnancy	Age (15–50), education, marital status occupation, income, parity, pregnancy planning, abortion history
Admasie *et al*. [35]	2014	Ethiopia (510)	Multigravidity, low educational level, presence of comorbidities, planned pregnancy, low educational level of health provider	Age, income, number of *ANC visits, hospitalization history, location of health facility
Molla *et al*. [37]	2017	Ethiopia (647)	Primigravid, first ANC visit was during 1st or 2nd trimester, number of ANC visits between 1–2, had a gynecological visit	-
Rouamba *et al*. [53]	2018	Burkina Faso (2371)	Urban residence, primigravid, first ANC visit was during 1st trimester	Age (14–50)
Obadeji *et al*. [32]	2020	Nigeria (369)	Age 30 yrs. or more, associated medical condition, low educational level	Marital status, gravidity, employment status

Table 2.3 *ANC: Antenatal clinics

2.3.3.2 Over-the-Counter Medication (OTC)

Easy and relatively uncontrolled access to OTC and herbal medicines may give the impression that these medications are safe to use even during pregnancy. However, many OTC products have an unknown safety profile in pregnancy while others, such as NSAIDs are known to be potentially harmful to the fetus [63].

Yusuff and colleagues found that 64% of participants used self-medication as a first response to any sickness rather than seeking medical advice. These practices were associated with the third trimester of pregnancy, low income, and long distance to health facilities. Furthermore, none of the participants knew the actual ingredients of the herbal medicines they used as it was usually purchased as preformulated products from the local market [28].

Mbarambara and colleagues found that self-medication practices were highly prevalent (61%) among their pregnant cohort. Explanations for high self-medication use included a previous experience with the same medicine, the non-serious and self-limiting nature of the condition being treated, and the cheap and easy access of such medicines. The most used medicines were paracetamol and amoxicillin. The provider of this medication was the pharmacist in 72% of cases in this study. Self-medication was more prevalent among women over 25 years of age. Most women were not aware of the potential risks of harm associated with self-medication, to either the mother or fetus [61].

In their study in Ghana Gbagbo *et al*. found that the main reasons for high rates of self-medication (69%) use was their easy accessibility, low cost, belief that the condition being treated was minor and the common perception that self-medication has little or no side effects. In their focus group discussions, level of education was a key determinant of self-medication with women with secondary and tertiary education claiming that they could read about their health conditions on the internet and then obtained medication without engaging with an antenatal practitioner or visiting ANC. Nevertheless, they found that regular antenatal visits did not mitigate self-medication use [41]. Moreover, the perception among 90% of self-medicating women that they did not experience any side effects and the high rates of first trimester use highlighted the need to educate them about the potential risks of medication use to the fetus.

Khalf *et al*. assessed the use of OTC medication among Libyan women, and they found that even though most of the participants (92%) do not trust in the safety of OTC medicines, the majority of pregnant women take them at least once throughout their pregnancy.[55].

2.3.3.3 Traditional and Herbal Medicines (THMs)

Around 70–95% of people living in developing countries use traditional medicines as part of their primary health care [65]. There is a dearth of data about the safety, specific composition, dosage of active ingredient, efficacy, contraindication, drug-drug interaction, and risks of adverse reaction including teratogenic effects, for most of these products. The pattern of use of such medicines and their safety in

pregnancy, particularly if provided via the informal health sector, is extremely difficult to investigate [66].

The prevalence of herbal medication uses in the reviewed studies ranged from 1–90% [60,58]. Malan and colleagues found that 90% of pregnant women reported the use of herbal medication as a complementary modality to prescribed medication. The plants used by these women were those that were widespread and easy to find as these women often maintained the plant in their home garden or from trees around the village [52].

The most used herbal medication included known plants like ginger and garlic [36]. However, unusual remedies such as soil from a mole hill or from Elephant dung were also reported [42].

In Africa, the use of THMs is rooted in ethnic and cultural beliefs and practices, which means such patterns of medication are integrated into daily life. In many cases, these medicines have a long track record of safety and, hence, are usually harmless. The reported reasons for use, and types, of THMs used during pregnancy differs according to geographical location and indication of use. Based on the studies reviewed, women in North African countries such as Egypt and Morocco reported using THMs to increase milk production or to get back into shape after delivery [44,54]. In Sub-Saharan countries, the indications range from include medical issues such as treating malaria [49,53,58]; gynecological issues such as facilitating childbirth [43], avoiding perineal tearing, preventing miscarriage [51]; for the baby's benefit such as

improving the well-being of the fetus or having a beautiful baby [52]; and protection of the mother and unborn baby from witchcraft [29].

2.4 Discussion

This review shows that medicine use is common practice among African pregnant women. Most studies explored THM and self-medication practices, which were reportedly widespread. The focus on these medicines and the findings of widespread use, are expected, given the limited access to health services, limited health worker training in rational drug use, widespread availability of THMs, and limited regulatory enforcement capacity in these countries.

Extrapolating general patterns of medicine use during pregnancy across Africa is challenging in the face of the differences in 1) location, time and methodology of the studies, 2) availability of health care services, and 3) varied socio-cultural contexts of populations studied. Such factors would be expected to influence the variation in prevalence, type, and associated factors of medication use.

It was difficult to compare the reviewed studies; few used ATC categories, whereas the majority categorized medications based on their therapeutic classes. Self-medication may include PM in addition to OTC and THM, although other research just includes OTC. Only one study utilized TGA classification to classify teratogenic medicine, whereas 11 used FDA risk classification.

Teratogenic medications mentioned in this review include a wide ranging. Some medications can be prescribed with caution if the benefits of use in the mother

outweigh the potential risk to the fetus. However, other drugs like as ciprofloxacin, tetracyclines, and warfarin can usually be substituted by safer (to pregnancy) medications such as penicillin, cephalosporins, and heparins.
Methodological variances, types of medications analyzed, disparities in health-care settings, and variations in pregnant women's knowledge, as well as prescriber's educational levels, might all contribute to the results discrepancy.

The most often reported medicines were antibiotics. This might be explained by their indication for the treatment of infectious disorders, including sexually transmitted diseases [59].

Interestingly, PM use was more prevalent in some rural areas, as seen in Ethiopia, possibly because health care providers failed to adequately counsel patients and access to PM was easier due to poor regulatory controls in these settings [34].

In an HIV-endemic setting like South Africa, Aviv and colleagues [17] did not report on the HIV prevalence of their cohort, as this study was conducted before voluntary counselling and testing for HIV and ARTs were available to patients in the public sector [17]. None of the studies assessed the impact of HIV on patterns of medication use.

Other studies' methodological strategies for antenatal medication use can help lay the groundwork for observational research by demonstrating 1) different sampling techniques for identifying pregnancy trimesters, 2) accurate calculation of period of exposure, and 3) methods of soliciting information on medication use. Some studies

used self-report while some only looked at medical records and others used a combination of both. In reviewed studies, only Rouamba *et al.* and Potchoo *et al.* describe how they calculated timing of medicine exposure in this review [53,56]. The lack of access to routine ultrasound for gestational dating in Africa poses a significant challenge in estimating the gestational age at which reported medicines exposures are likely to have occurred [64].

Some studies found an association between multigravidity (which is also strongly correlated with age) and prescription medicine use. However, there was an inverse relationship in other studies where primigravid women were more likely to be prescribed a prescription med. These findings could be a function of access to care and treatment-seeking behaviour in different types of settings. Factors such as reduced ability to access care for themselves among multigravid women and lower tolerance for the physiological changes that occur during pregnancy among primigravid women are some of the complex web of factors that influence medicine use patterns among pregnant women [37].

Based on the studies included in this review, a considerable proportion of pregnant women in Africa are intentionally practicing self-medication during their pregnancy. The high prevalence of self-medication with OTC or herbal medicines could be explained by distances to public health facilities, the unaffordability of accessing appropriate care and perceptions of inadequate service delivery and poor quality of care at formal health facilities [28].

Among the most used medicine categories were supplements and vitamins. They are routinely dispensed at ANC visits as a standard of care due to their known benefits in the preconception and antenatal period. Haematinics (iron, vitamin B12, and folic acid) were understandably identified as the most frequently prescribed treatment, given the high rates of anaemia in pregnancy in low-middle income countries, particularly in Africa [30,68].

One of the key issues noted in this review is that what are prescribed medicines in some countries are OTC in others: amoxicillin is considered an OTC medicine in some countries, such as eastern of DR Congo. The provider of this medication was the pharmacist in 72% of cases in this study [61].

Traditional medicines are seldom covered by government policy. Due to differences in definition and categorization of traditional medicine therapies, regulating traditional medicine items, practices, and practitioners is challenging. People in rural regions rely on TM to address their primary health care requirements since these medications are easily accessible and often free [42].

2.5 Conclusion

This review highlighted the complexity of understanding medicine use in pregnant women in Africa and the dearth of data on the impact of such medicine use on both maternal and fetal health. There is an intricate interplay between maternal factors such as socioeconomic status, age, parity and comorbidity, health system factors such as access to health care, clinical oversight and medicines and cultural factors. Studies such as these provide much needed information on the factors that influence

medicine use among pregnant women and the possible risk of harm to which they may be exposing themselves and their infants.

A clear recommendation that can be made from this review is the need to standardise the methodology and reporting of drug utilisation among studies focussing on medicine use in pregnancy. Developing standardised approaches to reporting timing of exposures, interviewing techniques to elicit reliable exposure information and coding of medicines are some of the areas where harmonisation of approaches will be beneficial. This data can be used to help develop strategies for better prescribing practices while identifying priority medicines for teratovigilance research. The ability to achieve this goal is greatly hampered if studies are subject to significant bias, confounding and problems with internal validity; if the data are not generalizable to the populations of interest; or if there is insufficient reporting that prevents meaningful interpretation or comparison of results. We propose that future research consider the following recommendations, based on the current state of evidence:

1.Development of standard methodologies for assessing medicine use in pregnancy: There is indeed a wide variation in published studies on medicines use during pregnancy. This heterogeneity makes it difficult to compare studies and limits their utility in informing policy and program development. Research groups across the globe should collaborate to develop guidelines for measuring medication use during pregnancy. A gold standard like this would help define databases, sampling methods, inclusion, and exclusion criteria, calculating gestational period of exposure, and classification and coding of medications.

2.Standardised classification of teratogens: With the replacement of the traditional FDA pregnancy classification of medicines, classification of teratogens should be reliant on a vetted source of such information and the timing of exposure during pregnancy. Information reflected in reliable data sources such as the Summary of Product Characteristics (SPC) or Product information approved by mature regulatory authorities such as the FDA or EMA will support a more standardised and realistic classification of teratogenic exposures during pregnancy.

2.6 Scope of the Study

Study Aim

The study aimed to describe and compare the self-reported pattern of medicine use during pregnancy in a cohort of pregnant women living with or without HIV, seeking care at Gugulethu antenatal facility in Western Cape South Africa.

Objectives

The study aim was accomplished by the following study objectives:

1) To describe the type and extent of medicines used by various categories:
   - Type: prescription, over-the- counter, and traditional/herbal
   - Anatomical Therapeutic Chemical (ATC) classification (where relevant),
   - known teratogenic potential
   - the timing of exposure in relation to gestational age
2) To assess associations between extent and type of medicine use and:
   - HIV status
   - age
   - educational status
   - employment status
3) To describe the nature and frequency of self-reported suspected adverse reactions to treatments.

CHAPTER 3: METHODOLOGY

3.1 Study Setting and Design

This is a secondary analysis of data from the 'B Positive' study cohort project, a prospective observational cohort of pregnant women and their infants which was followed between January 2017 and July 2018 **(Figure 3.1)**. This analysis is confined to assessing self-reported medicine use in pregnant women living with or without HIV were enrolled at Gugulethu Midwife Obstetric Unit (MOU). This facility is a large primary health care facility in a low-income peri-urban township area of Gugulethu in Cape Town, South Africa. The MOU provides basic antenatal and obstetric services for pregnant women. The antenatal prevalence of HIV in Gugulethu has been reported at approximately (30%) [66]. The high prevalence of HIV allowed for rapid enrolment of pregnancy women living with HIV as well as a control group of pregnant women not living with HIV

3.2 Study Population

Pregnant women aged 18 years or older living with or without HIV seeking care at Gugulethu MOU for their first antenatal visit were enrolled in the study. Women were eligible if they were able to provide informed consent, their first antenatal visit was at Gugulethu MOU, their HIV status was confirmed by routine testing, and they planned to reside with their babies within Cape Town at least one year postpartum. Women were excluded if they presented at the facility for the first time in active labour.

3.3 Data Collection

All participants were interviewed face-to-face one to three times during the antenatal period, depending on the gestational age (GA) at enrolment. Ultrasound was used to measure GA during the first prenatal appointment, and it was used to calculate the estimated pregnancy start date and GA at subsequent antenatal sessions and at birth. All face-to-face interviews took place around routinely scheduled antenatal or postnatal clinic visits. Additional short telephonic interviews took place and were used to collect basic data on maternal and infant health as well as to maintain participant contact over time.

Interviews were conducted by trained field workers, working in the predominant local language, isiXhosa, in a private space adjacent to the Gugulethu MOU. Questionnaires collected data on basic demographic information, obstetric and medical history, alcohol use, medication use, indication of use and side effects experienced.

3.4 Ethical Considerations

The protocol was reviewed and approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (UCT FHS HREC), registration number (REF 111/ 2021, **Appendix 1**). The research is a descriptive analysis of prospectively collected medication histories which was approved under the overarching B Positive research protocol (REF 541/ 2015 and 749/ 2015, **Appendix 2**). All participants of the prospective cohort were consented at enrolment. Data from the cohort study has been stored in a password protected REDCAP database and only anonymised extracts of the data were used for this sub-study. Confidentiality

was maintained with access to the data limited only to the investigators. Laptops in which the anonymised data is stored were protected and only accessible to the investigators and protected and stored in the Clinical Pharmacology Department in a locked office and locked drawer when not in use.

3.5 Data Analysis

Medicine exposure data were manually cleaned and coded into the type of medicines (PM, THM or OTC) relevant Anatomical Therapeutic Chemical (ATC) level 1 and level 2 categories by a medical doctor (the master's candidate) and a pharmacist (the candidate's primary supervisor). Potentially unsafe medicines were classified according to the TGA classifications system [70]. Medicine exposures that were reported to have stopped at least 2 weeks before the pregnancy estimated start date were excluded from the exposure analyses. Non-medicinal product use (coffee, milk, hot water) was classified as "non-medicinal exposures". Moreover, medicine names that were unclear or reported as unknown by the participant were classified as "medication unknown".

Data were analysed using Stata 14.0 (Stata Corporation, College Station, TX, USA). Maternal demographics were reported by using descriptive statistics stratified by HIV status. This study assessed the use of prescription, OTC, and THMs. 95% confidence intervals were calculated for all types of medicines exposures and reported as a percentage of the entire cohort as well as the specific subgroup being compared (HIV status, age category, and employment status). Given that most HIV-infected women were on antiretroviral treatments, prescription medicine use was reported including and excluding antiretroviral medicine use. Similarly, given the

widespread and recommended use of iron, folate, and calcium supplementation, OTC medicine use was reported with and without inclusion of vitamin and mineral supplements. The two-sided Fisher's exact test was used to analyze categorical variables which were also expressed as percentages in the data tables. A p value <0.05 was considered statistically significant.

CHAPTER 4: RESULTS

4.1 Demographic Information of Study Population

The sample included 989 pregnant women, 510 pregnant women living without HIV (PWLO HIV) and 479 Pregnant women living with HIV (PWLW HIV). Women who had an ectopic pregnancy (n=3) or an elective termination of pregnancy (TOP) (n=4) were excluded from this analysis. The final sample size included 982 pregnant women, of which 507 PWLO HIV and 475 PWLW HIV.

Table 4.1 describes the cohort demographics and compares clinical characteristics between PWLW HIV and PWLO HIV at their first ANC visits. Over half of the participants 528 (54%) were below 30 years old - mean age was 29 years (SD ±6). In terms of their educational status, 915 (93%) women had completed secondary education. Almost half 432 (44%) of respondents were married and 550 (56%) were single. More than half of the participants 564 (57.4%) were unemployed. Six hundred (61.2%) of the respondents first sought antenatal care in the second trimester of gestation. The majority of the pregnant women 590 (60%) had a normal vaginal delivery and 911 (92.8%) had a livebirth, with 19 sets of twin births. A history of chronic illness other than HIV was reported by 122 (12.4%) pregnant women. PWLW HIV had a higher rate of hypertension 20 (4.2%) compared to PWLO HIV 15 (3.0%).

Table 4.1 Socio-Demographic Profile of Study Population

Characteristics	Overall n (%)	PWLO HIV n (%)	PWLW HIV n (%)
Maternal age (years)			
≤ 24	238 (24.2)	170 (33.5)	68 (14.3)
25-29	290 (29.5)	156 (30.8)	134 (28.2)
30-34	255 (26.0)	108 (21.3)	147 (31.0)
≥ 35	199 (20.3)	73 (14.4)	126 (26.5)
Education			
Primary	44 (4.5)	17 (3.4)	27 (5.7)
Secondary	915 (93.2)	472 (93.1)	443 (93.3)
Tertiary	23 (2.3)	18 (3.6)	5 (1.1)
Marital status			
Married/co-habiting	432 (44.0)	219 (43.2)	213 (44.8)
Not married/ non-cohabiting	550 (56.0)	288 (56.8)	262 (55.2)
Employment			
Attending school/college	69 (7.0)	51 (10.1)	18 (3.8)
Formal employment	345 (35.1)	166 (32.7)	179 (37.7)
Informal employment	4 (0.4)	3 (0.6)	1 (0.2)
Unemployment	564 (57.4)	287 (56.6)	277 (58.3)
Parity			
0	247 (25.2)	166 (32.7)	81 (17.1)
1	330 (33.6)	168 (33.1)	162 (34.1)
≥2	405 (41.2)	173 (34.1)	232 (48.8)
Pregnancy outcome			
Live birth	911 (92.8)	469 (92.5)	442 (93.1)
Miscarriage	19 (1.9)	12 (2.4)	7 (1.5)
Stillbirth	23 (2.3)	13 (2.6)	10 (2.1)
Neonatal death	9 (0.9)	5 (1.0)	4 (0.8)
Outcome unknown	20 (2.1)	8 (1.6)	12 (2.5)
Mode of Delivery			
Normal vaginal delivery	590 (60.1)	314 (62.0)	276 (58.1)
Emergency C/Section	180 (18.3)	101 (19.9)	79 (16.6)
Scheduled C/Section	120 (12.2)	63 (12.4)	57 (12.0)
Unknown	92 (9.4)	29 (5.7)	63 (13.2)
Trimester of enrolment			
First trimester	262 (26.7)	132 (26.0)	130 (27.4)
Second trimester	601 (61.2)	308 (60.8)	293 (61.7)
Third trimester	116 (11.8)	66 (13.0)	50 (10.5)
Unknown	3 (0.3)	1 (0.2)	2 (0.4)

Comorbidities			
Tuberculosis	10 (1.0)	2 (0.4)	8 (1.7)
Diabetes Mellitus	16 (1.6)	11(2.2)	5 (1.1)
Hypertension	35 (3.6)	15 (3.0)	20 (4.2)
Heart Diseases	1 (0.2)	1 (0.1)	0 (0.0)
Asthma	26 (2.7)	12 (2.4)	14 (3.0)
Epilepsy	3 (0.3)	3 (0.6)	0 (0.0)
Thyroid diseases	8 (0.8)	5 (1.0)	3 (0.6)
Psychological or mental condition	8 (0.8)	4 (0.8)	4 (0.8)
Other conditions	15 (1.5)	13 (2.6)	2 (0.4)
Alcohol use (in current pregnancy)			
Yes	89 (9.1)	46 (9.1)	43 (9.1)
No	893 (90.9)	461 (90.9)	432 (91)

4.2 Prevalence of Medicines Practice During Study Period

Of 982 women in the study, OTC, at 907 (92.3%) use was the most prevalent medication reported, with PM, at 600 (61.2%) the next highest usage and THMs, at 36 (3.7%) only used by a minority of patients. Only 39 (4.0%) women did not report any medicine use during pregnancy. Some differences were observed in the patterns of medication use based on the women's HIV status. A much higher proportion of PWLW HIV use prescribed medication compared to PWLO HIV (93.5% vs. 31.0%; p=0.001), largely due to high ART coverage. When ART treatment was excluded from the analysis, prescription medicine use was similar across both groups (approximately 30%). In contrast, PWLO HIV were significantly more likely to report using OTC products compared to PWLW HIV (77.7% vs. 56.2%; p<0.001). A majority of pregnant women reported using four or more medicines during the pregnancy 607 (62%). Interestingly, when we excluded ART and supplements and vitamins, PWLO HIV were statistically significantly more prone to use more than four medicinal products during their pregnancy compared to PWLW HIV (26.8% vs.18.9% ; p=0.003). More PWLW HIV used four or more medicines during their first trimester in comparison to PWLO HIV (13.6% vs 23.2%; p<0.001), however, when ART and supplements were excluded, the rates of polypharmacy in the first trimester were similar in both groups (**Table 4.2**).

The medicines reported to be used during the pregnancy were classified by the ATC classification system up to level 2. The most frequently used medicines during pregnancy were anti-anaemic (77.2%), analgesics including paracetamol and aspirin (54.4%), antivirals (45%), drugs for acid related disorders (18%) and systemic

antibacterial agents (10.4%), as presented in (**Table 4.3, Figure 4.1**). Approximately 13% of medicines reported were not clearly named by the participants.

Of the study participants, 3.7% reported using (THMs) during pregnancy**.** Although not quite reaching conventional statistical significance, more PWLO HIV reported using THMs compared to PWLW HIV (4.7% vs 2.9%; p=0.07). **Figure 4.2** lists the number of times specific THMs were reported to have been used by pregnant women during the course of their pregnancy. Holy water and a product called Umchamo wemfene (literally translated as Baboon's Urine) were the most commonly reported products used among the cohort (**Figure 4.2**). Stameta (an aloe vera-based commercially) available product widely used for menstrual disorders as well as gastrointestinal disorders including constipation, was used by 28 (9.0%) pregnant women in this analysis [71,72].

Table 4.2 Proportion of Women Taking at Least One Type of Medicine by HIV Status

Type of medication used	Overall 982 n=982 (%; 95% CI)	PWLO HIV n=507 (%: 95% CI)	PWLW HIV n=475 (%; 95% CI)	p value
Prescription Medicine (including ARVs)	601 (61.2; 58.1–64.2)	157 (31.0; 26.9–35.0)	444 (93.5; 91.3–95.7)	p<0.001
Prescription Medicine (excluding ARVs)	299 (30.5; 27.6–34.4)	153 (30.2; 26.3–34.3)	144 (30.3; 26.3–34.6)	p=0.96
Over-the-counter (OTC) Medicine (including supplements & vitamins	907 (92.3; 90.5–93.9)	394 (77.7; 73.9–81.3)	267 (56.2; 51.7–60.7)	p<0.001
OTC medicine (excluding supplements & vitamins)	689 (70.2; 67.2–72.9)	371 (73.2; 69.1–76.9)	318 (66.9; 62.6–71.0)	p=0.03
Traditional and Herbal Medicines (THMs)	36 (3.7; 2.7–5.0)	24 (4.7; 3.2–7.0)	12 (2.9; 1.4–4.4)	p=0.07
Median number of medicines reported during pregnancy (IQR)**	4 (3–6)	4 (2–5)	5 (3–6)	p<0.001
No reported use of medicine*	39 (4.0; 3.1–5.6)	28 (5.5; 4.2–8.3)	11 (2.3; 1.3–4.1)	p=0.010
1	60 (6.1; 4.8–7.8)	36 (7.1; 5.2–9.7)	24 (5.1; 3.4–7.4)	p=0.181
2	111 (11.3; 9.6–13.6)	79 (15.6; 13.0–19.4)	32 (6.7; 4.6–9.1	p<0.001
3	165 (16.8; 14.6–19.3)	90 (17.8; 14.7–21.3)	75 (15.8; 12.8–19.4)	p=0.411
>=4	607 (61.8; 58.7–64.8)	274 (54.0; 49.7–58.3)	333 (70.1; 65.8–74.1)	p<0.001

Table 4.2 * This includes women who did not report any medication use during pregnancy, or reported only medicines used prior to pregnancy and those women who reported using substances that were not medicines (e.g. hot water, coffee drinks etc).
** Multi-ingredient products, including antiretrovirals, were counted as a single exposure.

Median number of medicinal products reportedly used during pregnancy (excluding ART & Supplements & vitamins)	2 (1–3)	2 (1–4)	2 (1–3)	p=0.188
No reported use of Medicine* (excluding ART & Supplements and vitamins)	197 (20.1; 17.7–22.7)	96 (18.9; 15.7–22.6)	101 (21.3; 17.8–25.2)	p=0.363
1	223 (22.7; 20.2–25.4)	108 (21.3; 17.9–25.1)	115 (24.2; 20.6–28.3)	p=0.277
2	178 (18.1; 15.8–20.7)	91 (18.0; 14.8–21.5)	87 (18.3; 15.1–22.1)	p=0.881
3	158 (16.1; 13.9–18.5)	76 (15.0; 12.1–18.4)	82 (17.3; 14.1–20.9)	p=0.333
>=4	226 (23.0; 20.5–25.8)	136 (26.8; 23.1–30.9)	90 (18.9; 15.7–22.7)	p=0.003
Median number of medicinal products reportedly used during first trimester	2 (0–3)	1 (0–2)	2 (1–3)	p<0.001
No reported use of Medicine*	259 (26.4; 23.7–29.2)	181 (35.7; 31.6–40.0)	78 (16.4; 13.3–20.0)	p<0.001
1	228 (23.2; 20.7–26.0)	96 (18.9; 15.7–22.6)	132 (27.8; 23.9–32.0)	P=0.001
2	177 (18.0; 15.7–20.6)	106 (20.9; 17.6–24.7)	71 (14.9; 12.0–18.5)	P=0.015
3	139 (14.1;12.1–16.5)	55 (10.8; 8.4–13.9)	84 (17.7; 14.5–21.4)	P=0.002
>=4	179 (18.2; 15.9–20.8)	69 (13.6; 10.9–16.9)	110 (23.2; 19.6–27.2)	P<0.001
Median number of medicinal products reportedly used during first trimester (excluding ART & Supplements and Vitamins)	1 (0–2)	1 (0–2)	0 (0–1)	p=0.035
No reported use of Medicine*	470 (47.9; 44.7–51.0)	226 (44.6; 40.3–48.9)	244 (51.4; 46.9–55.9)	p=0.033
1	248 (25.3; 22.6–28.1)	135 (26.6; 22.9–30.7)	113 (23.8; 20.2–27.8)	p=0.306
2	133 (13.5; 11.5–15.8)	71 (14.0; 11.2–17.3)	62 (13.2; 10.3–16.4)	p=0.663
3	65 (6.6; 5.2–8.4)	35 (6.9; 5.0–9.5)	30 (6.3; 4.4–8.9)	p=0.711
>=4	66 (6.7; 5.3–8.5)	40 (7.9; 5.8–10.6)	26 (5.5; 3.7–7.9)	p=0.131
Potential teratogenic exposure during pregnancy	300 (30.6; 27.7–33.5)	164 (32.4; 28.4–36.6)	136 (28.6; 24.7–32.9)	p=0.213

Table 4.3 Self-reported Medicine Use by ATC level 2 Classification

	ATC Category-Level 2	n (%)
A02	Drugs for acid related disorders	175 (17.8)
A03	Anticholinergics (anti-emetics)	15 (1.5)
A06	Laxatives	16 (1.6)
A07	Antidiarrheals	11 (1.1)
A10	Diabetic treatment	11(1.1)
A11	Vitamins	88 (8.9)
A12	Mineral supplements	13 (1.3)
B03	Anti-anaemic	758 (77.2)
C02	Antihypertensives	5 (0.5)
C03	Diuretics	17 (1.7)
C08	Calcium channel blockers	4 (0.4)
C09	ACE-inhibitors	9 (0.9)
C10	Lipid modifying agents	3 (0.3)
D01	Topical antifungals	1 (0.1)
D02	Emollients and protectants	43 (4.3)
D04	Antipruritic	37 (3.8)
D06	Topical antibiotics	3 (0.3)
D07	Corticosteroids, dermatological preparations	11 (1.1)
D08	Antiseptics	1 (0.1)
G01	Gynecological anti-infective and antiseptics	47 (4.8)
G02	Other gynecologicals	2 (0.2)
G03	Sex hormones and contraceptives	47 (4.8)
G04	Urologicals	15 (1.5)
H02	Systemic corticosteroids	5 (0.5)
J01	Systemic antibacterial	103 (10.4)
J02	Systemic antimycotics	1 (0.1)
J04	Antimycobacterial	12 (1.2)
J05	Antivirals	438 (44.6)
J07	Vaccines	3 (0.3)
M01	NSAIDs	46 (4.7)
N02	Analgesics including paracetamol and aspirin	538 (54.8)
N03	Antiepileptics	3 (0.3)
N05	Psycholeptics	3 (0.3)
N06	Antidepressants	3 (0.3)
P01	Antiprotozoals	75 (7.6)
P03	Ectoparasiticides	7 (0.7)
R01	Nasal preparations	44 (4.5)
R03	Drugs for obstructive airways disease	40 (4.1)
R05	Cough and cold preparations	81 (8.2)

Figure 4.1 Self-reported Medicine Use by ATC level 2 Classification by HIV Status

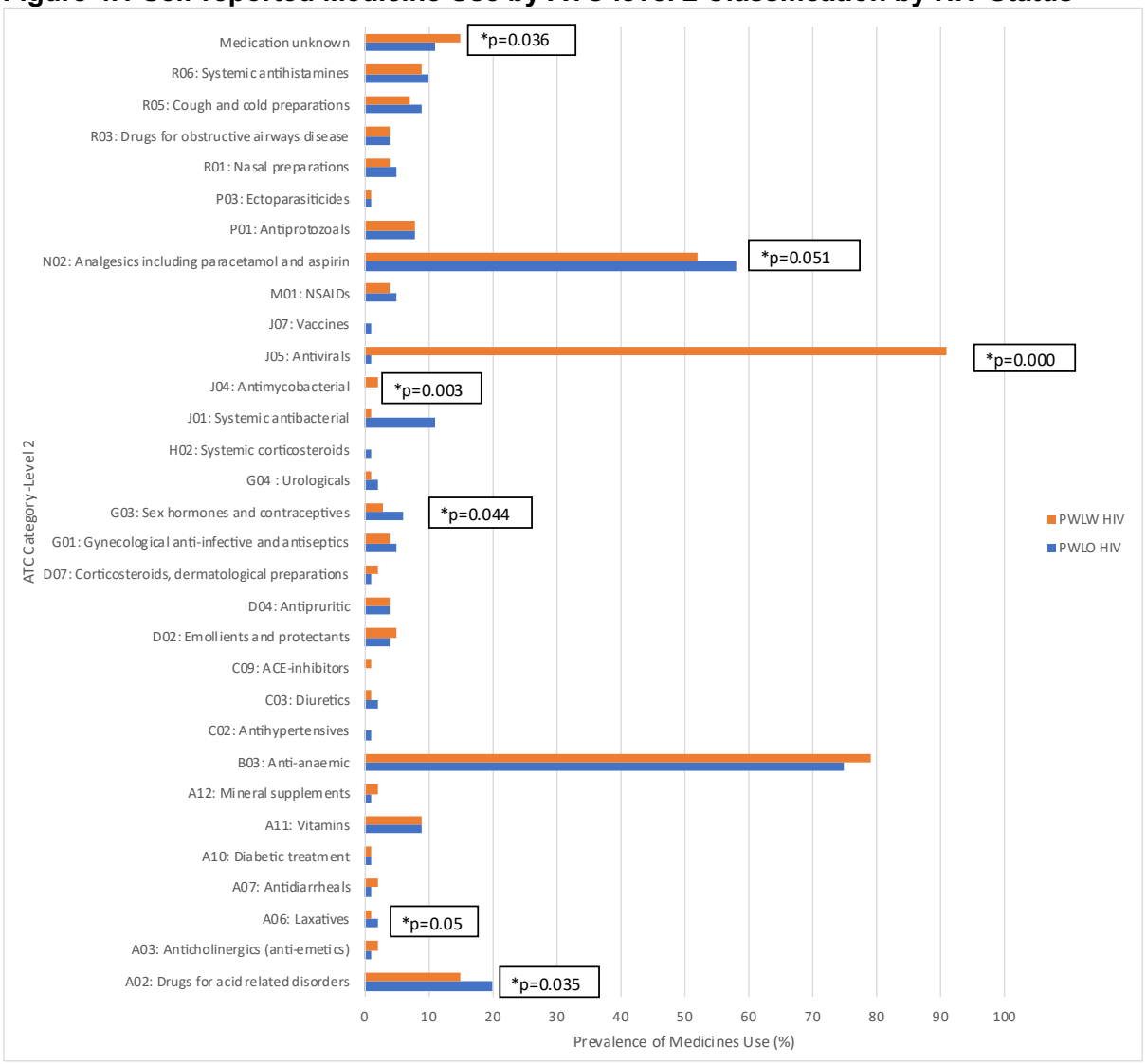


Figure 4.2 *p=significant p value

Figure 4.2 Top Ten of Traditional and Herbal Medicines (THMs) Reportedly Used During Pregnancy

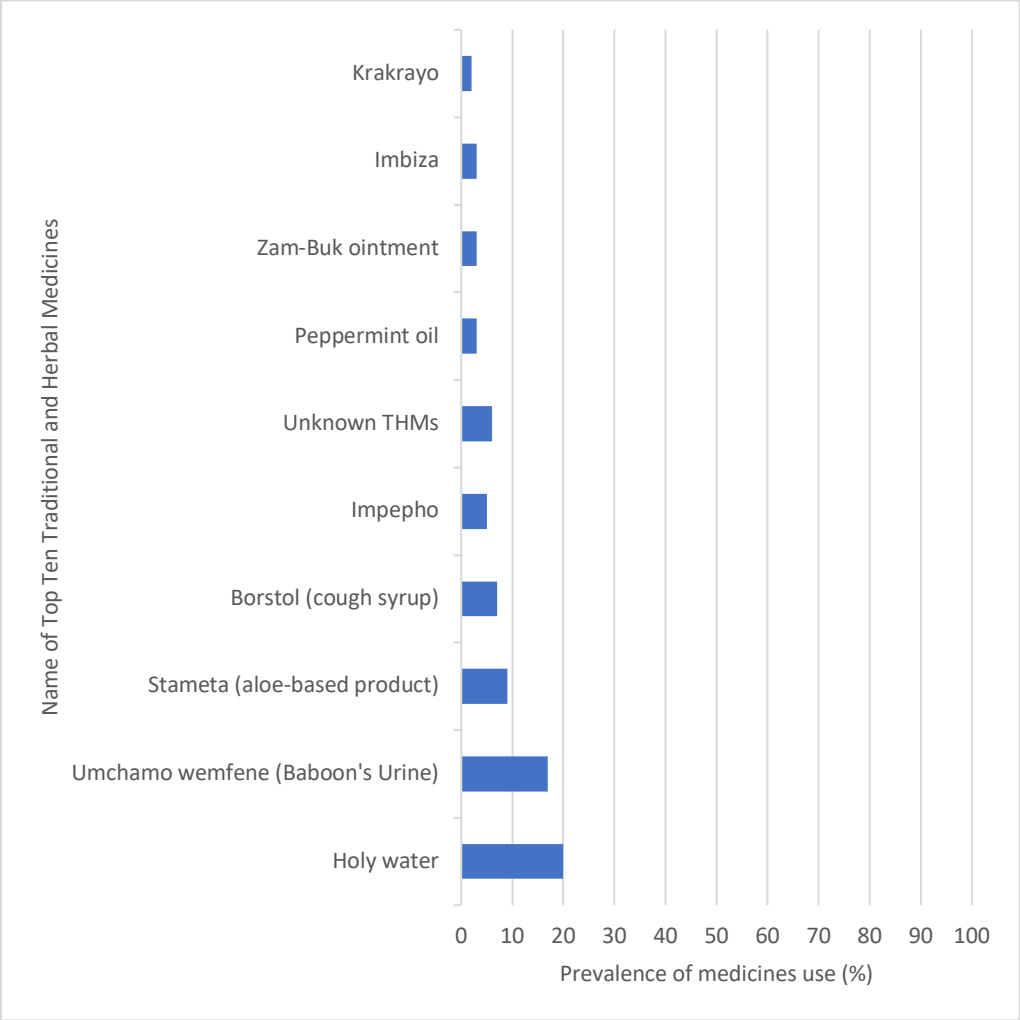


Table 4.2 THMs reported in this table per use not per women

4.3 Potentially Harmful Medicines

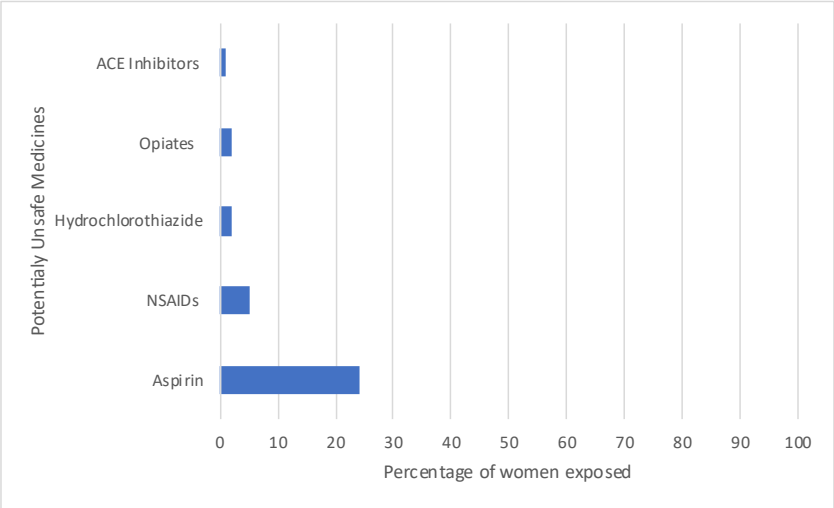
In total, we found 15 medications in use that could cause problems during various stages of pregnancy. Almost a third of the cohort, 300 (31%), reported using a potentially unsafe medicine during the course of the pregnancy (**Table 4.4**). The majority of unsafe medications used were from category C (those capable of causing harmful effects on the human fetus or neonate without causing malformations) followed by category D (suspected to have caused, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage), with only two women who reported using medicines from category X (high risk of causing permanent damage to the fetus) of the TGA classification system [70]. Aspirin (238; 24.2%), NSAIDs (46; 4.7%), hydrochlorothiazide (17; 1.7%) and opiates (17; 1.7%) were the most commonly reported potentially unsafe medicines used (**Figure 4.3**).

Table 4.4 Number of Women Exposed to Teratogenic or Potentially Unsafe Medicines by Trimester of Exposure

Name of teratogenic medicine	Trimester of risk	Australian Risk Category	Number of women exposed	First trimester exposure (T1)	Second trimester exposure (T2)	Third trimester exposure (T3)	Trimester of exposure unknown
Any teratogen	T1, T2, T3	C, D, X	300 (30.6%)	190 (19.4%)	208 (21.2%)	161 (16.4%)	40 (4.1%)
Aspirin(Doses of 100- 500 mg/day)	T1, T2. T3	C	238 (24.2%)	149 (15.2%)	168 (17.1%)	120 (12.2%)	20 (2.0%)
NSAIDs (ibuprofen, piroxicam, indomethacin, diclofenac)	T1, T2. T3	C	46 (4.7%)	21 (2.1%)	22 (2.2%)	17 (1.7%)	12 (1.2%)
Hydrochlorothiazide	T1, T2	C	17 (1.7%)	13 (1.3%)	14 (1.4%)	14 (1.4%)	4 (0.4%)
Opiates (tramadol, methadone)	T3	C	17 (1.7%)	5 (0.5%)	11 (1.1%)	12 (1.2%)	4 (0.4%)
ACE Inhibitors	T2, T3	C	7 (0.7%)	6 (0.6%)	6 (0.6%)	6 (0.6%)	1 (0.1%)
Doxycycline	T2, T3	D	4 (0.4%)	2 (0.2%)	1 (0.1%)	1 (0.1%)	2 (0.2%)
Trimethoprim-Sulfamethoxazole	T1	C	4 (0.4%)	2 (0.2%)	3 (0.3%)	3 (0.3%)	0 (0%)
Antidepressants (amitriptyline, citalopram, fluoxetine)	T3	C	3 (0.3%)	2 (0.2%)	2 (0.2%)	2 (0.2%)	0 (0%)
Simvastatin	T1	D	3 (0.3%)	3 (0.3%)	3 (0.3%)	3 (0.3%)	0 (0%)
Misoprostol	T1	X	2 (0.2%)	0 (0%)	2 (0.2%)	1 (0.1%)	0 (0%)
Risperidone	T3	C	2 (0.2)	2 (0.2%)	3 (0.3%)	2 (0.2%)	0 (0%)
Chlorpromazine	T3	D	2 (0.2%)	1 (0.1%)	2 (0.2%)	1 (0.1%)	0 (0%)
Fluconazole	T1	D	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)
Sodium Valproate	T1, T2. T3	D	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0%)
Phenytoin	T1	D	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0%)

Table 4.4 End of trimester 1 calculated by adding 97 days to pregnancy start date and end of trimester 2 calculated by adding 195 days to pregnancy start day. **Category C**: medication that, due to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations, Those effects may be reversible. **Category D**: medication that have caused or are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. **Category X:** medication with high risk of causing permanent damage to the fetus that should not be used in pregnancy or when there is a possibility of pregnancy exists [70].

Figure 4.3 Top Five of Teratogenic or Potentially Unsafe Medicines Reportedly Used During Pregnancy



4.4 Factors Associated with Medicines Use

When we assessed the association between age, employment status, and maternal educational level, there was a direct correlation between age and medication use; pregnant women over 35 years old being at highest risk of PM use during the pregnancy (**Table 4.4**)**.** Similarly, employment status showed association with medicines use. Pregnant women who classify their employment status as students (attending school/college) were more prone to use PM during pregnancy (**Table 4.5**)**.** On the other hand, maternal level of education had no association with medication use (**Table 4.6**).

Figure 4.4 Self-reported Use of Medicinal Products by Pregnant Women by Maternal Age Category

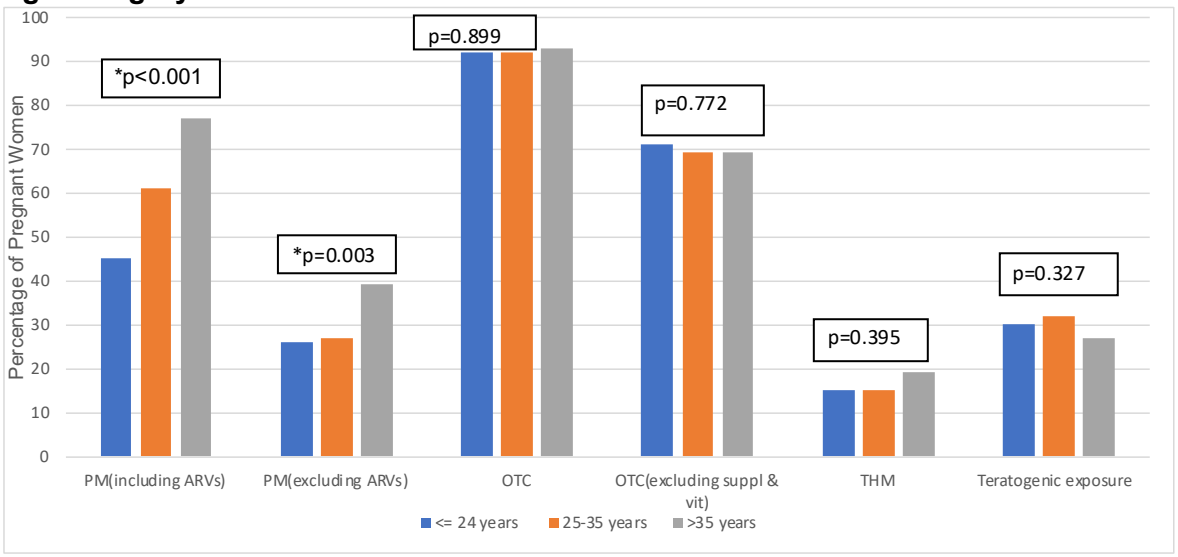


Figure 4.4 *p=significant p value

Figure 4.5 Self-reported use of medicinal products by Pregnant Women by Employment Status

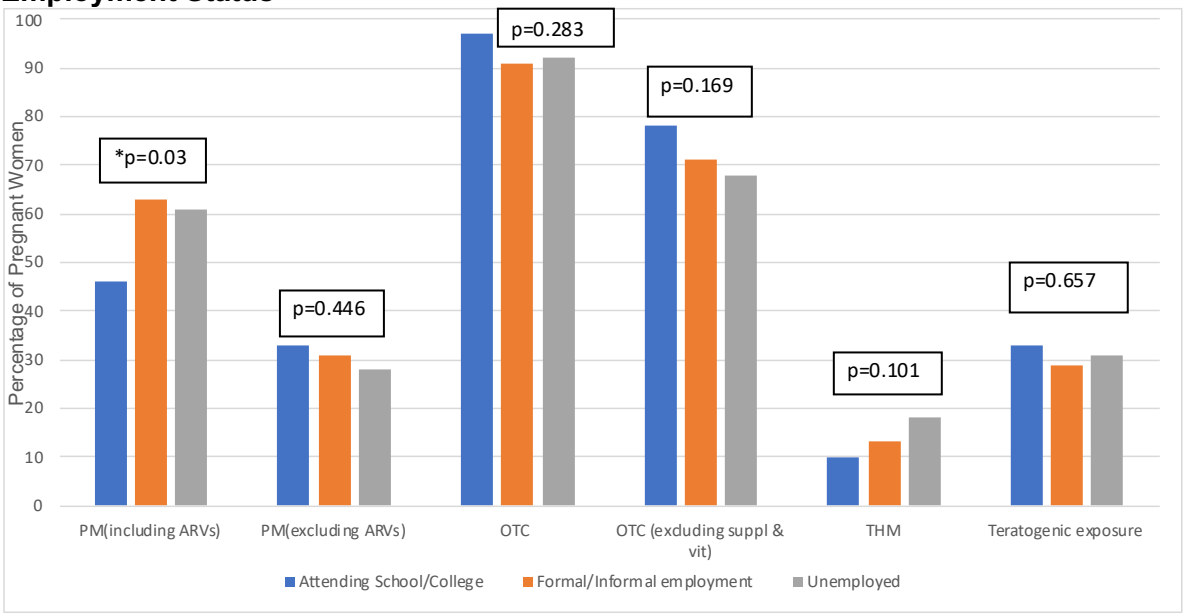
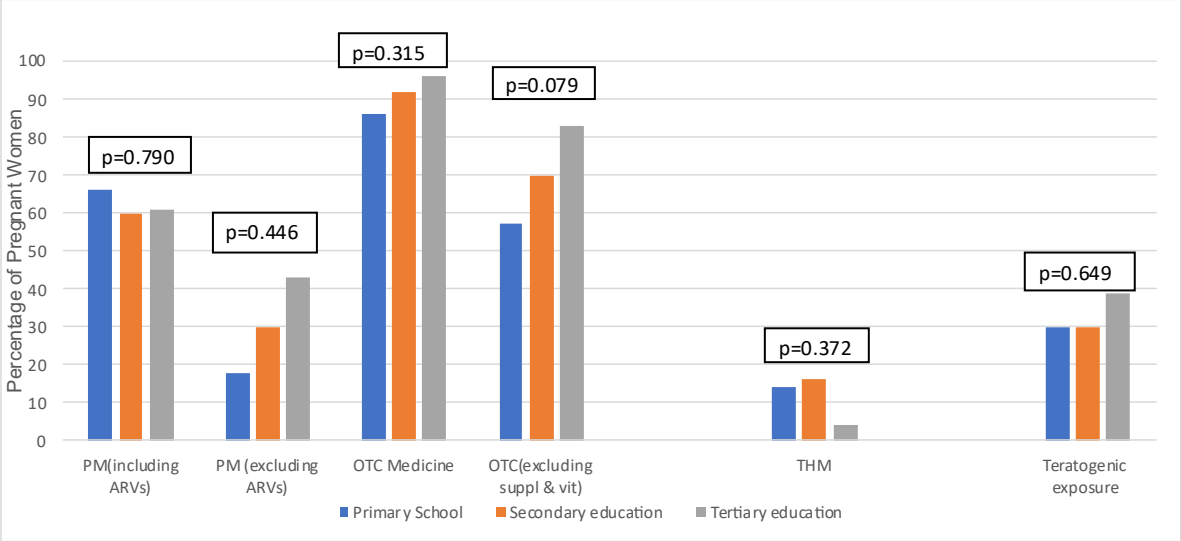


Figure 4.5 *p=significant p value

Figure 4.6 Self-reported Use of Medicinal Products by Pregnant Women by Maternal Level of Education Completed



4.5 Side Effect Profile

Side effects experienced by pregnant women were minimally reported. Among the 601 women who reported using prescribed medicines, only 15 (2.5%) reported experiencing a side effect. About six (0.7%) and one (2.8%) of pregnant women reported side effects of OTC and THMs respectively (**Table 4.5**). Of PM, contraception and ARV were reported to have a side effect. Antihistamine, supplement and vitamins, and analgesics and antipyretics were reported OTCs with side effects. Umchamo wemfene (Baboon's Urine) was the only THMs reported in this profile.

Table 4.5 Experienced Side Effect

Side effect	Frequency (n)	Suspected medicine
Not mentioned	9	ARV (n=6) Contraception (n=2) Analgesics and antipyretics (n=1)
Dizziness	6	ARV (n=4) Supplement and vitamins (n=2)
Nausea	4	Supplement and vitamins (n=2) Antihistamine (n=1) Contraception (n=1)
Vomiting	2	ARV (n=1) Umchamo wemfene (Baboon's Urine) (n=1)
Skin itching	1	ARV (n=1)

The results presented in this chapter have fulfilled all the objectives that were established for this study.

CHAPTER 5: DISCUSSION

In this study we present an analysis of self-reported medicines use among 982 pregnant women living with and without HIV, attending antenatal care in an urban primary health facility in Cape Town, South Africa. This is the first study we are aware of, which compares self-reported medicine use among pregnant PWLW HIV and PWLO HIV.

5.1 Types and Extent of Medicine Use

All women except 39 (4%) reported taking at least one medicine during the course of their pregnancy. Over-the counter medicines were the most commonly reported type of medicines (92%) followed by prescription medicines (61.2%) and then traditional and herbal medicines (3.7%).

Prescription medicine use among pregnant women was found to be (61%) in this study, which is similar (59%) to a prior study conducted in Cape Town, South Africa by Aviv *et al.* (1993) [17]. However, in comparison to similar research conducted in other African countries [30,32,35,37,50], the current study's finding suggests a lower prevalence of self-reported prescription medicines use, but it is greater than the prevalence reported by Sevene *et al*. in Mozambique [59], Kazeem A Oshikoya *et al*. in Nigeria [30] and Mohammed *et al*. in Ethiopia [34]. In the current study, the high incidence of prescription medicine use is substantially due to almost half the cohort being treated with ARVs for HIV. This included 4 PWLO HIV who were taking ARVs for pre-exposure prophylaxis (PrEP), a trend which is likely to increase with regional guidelines supporting PrEP in pregnancy [73]. It is very likely that this prescription medicine use is an under-estimate due to incomplete reporting by women. This is

evident from the fact that in many cases in this study women were only able to recall one or two of the three ARVs that they were taking.

The results of this study showed that most (92%) of the pregnant women reported using OTC medicines including essential supplements to support a healthy pregnancy. The rate of OTC usage in this study, even when excluding vitamin and mineral supplements (70.2%) was greater than that observed in Ethiopia (52%) [34], Egypt (4%) [45] and Libya (31%) [55]. In other studies, the high prevalence of OTC use has been attributed to a variety of reasons, many of which are likely to apply here as well. Women may consider the condition to be self-limiting and non-serious, not requiring a costly consultation with a health care provider, past familiarity with the medicine, easier access to the OTC without a prescription, and a belief that OTC products are likely to be reasonably safe [17,28,41,61]. The most often utilized OTC medications were used to treat or prevent conditions that are commonly encountered during pregnancy including anti-anaemic medications for anaemia, multivitamins and minerals including folic acid to promote fetal health, antacids for heartburn, analgesics for muscular aches and pains, laxatives for constipation and cold and flu preparations.

In this analysis only 36 (3.7%) women reported using THMs during the course of their pregnancy, which is extremely low compared to rates reported in other studies in Sub-Saharan Africa which reported (90%) in Côte d'Ivoire [52], (80%) in Mali [58], (73%) in Ethiopia [36] and (67%) in Nigeria [27]. The discrepancies in these findings might be explained by differences in study design and the sample population which included many women also accessing care for HIV at an urban primary health

facility. Elrahim D. Haggaz *et al*. in Sudan reported that (1%) of the pregnant women in their study used herbal medicines [60]. The lower incidence of THMs usage in our research group might be explained by their higher level of education than in other studies, urban setting, the high proportion of HIV-infected individuals who may have been cautioned against using THMs as part of their ART adherence counselling, and underreporting. Note also the slightly lower percentage of THM use in PWLH HIV (2.5%) compared PWLO HIV (4.7%), p=0.0066. Variations in the approach to questioning, concerns about the potential for negative perception by study personnel and the influence of imperfect recall may also contribute to the low reporting rates of THM use in this cohort.

It is likely that many respondents did not report their use of THMs because it was considered part of their cultural beliefs and daily practice rather than a medicine by itself. This is reinforced by the fact that Holy water was the most commonly mentioned THM. Other barriers to reporting medication use have been explored by Allen and colleagues who found that because of the potential for unfavourable reactions, women reported concern about disclosing their use of traditional, OTC medicines and alcohol to antenatal personnel [75]. Further studies are required employing other questioning techniques including focussed group discussions and in-depth interviews to understand the factors that influence how women report medicine use [75].

Among ATC classification, anti-anaemic (77.2%), analgesics including paracetamol and aspirin (54.4%), antivirals (45%), drugs for acid related disorders (18%) and systemic antibacterial agents (10.4%) were the most frequently used medicines

during pregnancy (**Table 4.3**). A similar prescribing pattern has been reported in Nigeria [30], with ATC group B (medicines for blood and blood forming organs 48.6%; with anti-anaemic 45.5% being the most prescribed from this group), followed by ATC group N (medicines for the nervous system 13.8%; predominantly paracetamol 8%) and anti-infectives for systemic use (9.5%). In contrast, this finding is not similar to reports of a previous study conducted in Burkina Faso [53], which found that antimalarials (35%) and antibiotics (20%) were the most frequently used classes. These differences in patterns of medicine use in pregnant women across regions in Africa reflects the diversity of underlying conditions and comorbidities, access to medical care, prescribing and self-medication practices across the continent and the importance of exercising caution when extrapolating such medicine use practices across geographical sites.

When assessing medicines use based on the gestational age of the pregnancy we found that 23.2% of pregnant women used at least one medicinal product during the first trimester (Table 4.2). It was difficult to compare our findings to other studies due to methodological mismatch. Abubakar *et al*. reported that (11.1%) of the total medicines were prescribed during the first trimester [31]. Rouamba *et al*. found that of the total 4279 medicines used by pregnant women, 1492 medicines (34.9%) were used in the first trimester [53].

5.2 Potentially Harmful Medicine Exposures

A further noteworthy finding was that (30.6%) of our study population reported being exposed to potentially unsafe medicines during the course of the pregnancy. This finding is consistent with a study done in Burkina Faso which found that the

proportion of women taking potentially risky medicines during their pregnancy was (39%), the most frequently used medications in this group were quinine (22.6%), neomycin (0.4%), diazepam (0.4%), and ibuprofen (0.2%) [53].

The majority of potentially harmful exposures were reported to have occurred in the second trimester. Aspirin (24.2%), NSAIDS (4.7%), hydrochlorothiazide (1.7%), opiates (1.7%), and ACE Inhibitors (0.7%) were the most often used potentially unsafe medicines. Obadeji *et al*. also found that NSAIDs prevalence was 4.6% [32]. However, the results of NSAIDs prevalence in this investigation was higher compared to those reported in other studies [45,53].

Aspirin exposure was particularly high (24.2%) compared to many other studies [29,33,50] but Kebede *et al*. found that aspirin was also among the most used unsafe medicines in addition propylthiouracil, warfarin, enalapril and sodium valproate in their Ethiopian study [33]. Also in Ethiopia, Mohammed *et al.* reported different potentially harmful medication, which was fluoroquinolones (4.4%), atenolol (3.5%), tetracycline (2.7%) and efavirenz (0.9%) [34]. Kodhiambo also reported high rates of NSAID (13.6%), narcotic analgesics (12.4%), aspirin (5.6%) and anticonvulsants (0.8%) [50] use in their Kenyan cohort. Differences in results reported could be explained by the method and timing of exposure ascertainment, different profiles of comorbidities among women included in different studies, differences in the level of care at which women were seeking care, access to medicines as well as the classification system used to code potentially unsafe medicines.

In this analysis there was at least one valproate and one phenytoin exposure. The high use of valproate in women of child-bearing age has been identified as a

problem in the Western Cape [8]. In many circumstances, aspirin was used as analgesic when paracetamol would be more appropriate, as aspirin (doses of 500 mg/day and above) has been classified as a potentially unsafe medicine [74]. The frequent use of aspirin, opiates, and NSAIDS, which are considered more unsafe than paracetamol, highlights the need for improving medication safety literacy among both women and their care providers. In addition to aspirin and NSAIDS at least 15 (1.5%) women reported exposure to prescription medicines which are either category D or X medicines according to the TGA classification. This includes neuropsychiatric treatments such as sodium valproate, phenytoin, lithium and risperidone, which are known teratogens associated with significant risks to the fetus during pregnancy. Moreover, two women reported using misoprostol, a known abortifacient in the second and third trimesters of pregnancy.

While the safety profile of many of the THMs is not known, one commonly reported product called Stametta, an aloe vera-containing tonic and laxative, is known to be potentially unsafe in pregnancy. This product has also been anecdotally used as an abortifacient in Africa [71,72]. The high rates of potentially unsafe medicines use further support the need for improved training in therapeutics among midwives, providing them with resources that support safe and rational prescribing in pregnancy and communication techniques that encourage pregnant women to self-report the medicines exposures reliably.

5.3 Association Between Medicine Use and HIV Status, Employment Status and Level of Education

Prescription medicine use other than antiretroviral treatment was similar across HIV-status groups. The study found that PWLO HIV are more prone to self-medicating with OTC compared to PWLW HIV.

The present study confirmed the findings seen by others of a significant association between medicines use during pregnancy and older maternal age (p=0.011) (Figure 4.4) and those currently attending School/College (p=0.013) (**Figure 4.5**) [32,41] compared to those who are employed or unemployed. However, when assessing the level of education completed, no significant differences were seen in self-reported medicine use. The possible reasons for these findings is that as the maternal age increases, risk of maternal illness increases. The finding that women who are currently enrolled in an educational institution are more likely to utilize medications might be explained by their easy access to the internet, where they can learn about their medical condition and then order medication or because of regular follow-up and additional prescriptions in each appointment, or because they have a better literacy in pharmaceutical names and are therefore better able to recall the medicines they have taken. These trends in association would need to be validated across a wider, more diverse cohort of pregnant women.

5.4 Self-Reported Adverse Reactions

Our results showed minimal information about the side effects experienced by pregnant women. This might be because of the complexity of attributing the cause of signs and symptoms to a particular event or treatment and a possibly low level of

suspicion that any new event could be due to medicines intended to treat ill health. These data demonstrate a knowledge gap in appreciation of the risk- benefit profile of medicines, emphasizing the importance of developing interventions aimed at providing maternity staff, pregnant women, and women of child-bearing age with a better understanding of how medicines work and how to detect, monitor for and report adverse effects.

5.5 Study Strengths

This is the first study we are aware of that specifically assesses the differences in self-reported medicine use between PWLW HIV and PWLO HIV. Gestational dating was based on antenatal ultrasonography performed at the first antenatal visit, providing reliable estimates of timing of medicinal exposures. The study explored all kinds of medicine exposures including prescription medicines, OTC and THMs. The sample size was large to provide meaningful estimates of self-reported medicine use.

5.2 Study Limitations

There are limitations relating to our analysis. The study was conducted in a single health facility in South Africa and therefore raises concerns about the generalizability of the findings to other settings including rural settings and in similar settings in other parts of the country. Given that Gugulethu's antenatal care is a basic antenatal care site, it is likely that the sample was biased away from women with underlying risk factors and comorbidities, as these could have directly sought care at referral facilities. Nevertheless, women in this cohort who were subsequently referred to a

secondary or tertiary level facility would have been included and followed up even if antenatal care was continued elsewhere. Therefore, we believe that the sample is fairly representative of the local adult population of pregnant women who routinely seek care at this facility. Given that most women only sought care in the second trimester, it is likely that recall bias would have resulted in underreporting of medicine use, particularly short-term treatments, in the early stages of the pregnancy.
The interview process at each of the study visits was intensive and could have resulted in reporting fatigue, particularly at follow-up visits.

A key limitation of this study is that it only reports on self-reported medicine use. We did not seek to assess the completeness of self-reported use by comparing this to the clinical maternity case records, facility-based treatment registers, or the electronic pharmacy management system.

The questionnaires were administered by at least 4 different field study personnel who were not knowledgeable in the multitude of medicines reported. Therefore, incorrect spelling and missing names was a challenge that was addressed by involving a pharmacist and medical doctor in the subsequent data cleaning, coding, and classification of the medicines.

Regarding herbal and traditional medicines, we did not collect data on plant type, herbal medicines preparation, quantity consumed, frequency of intake, beliefs that impact medication usage, and the safety profile of these products. Many of the THMs are manufactured and sold as retail pharmaceutical products. It is likely that there

may be significant underreporting of home-made herbal remedies and remedies provided by informal traders and traditional healers.

Despite being included in the questionnaire, information on the indication for use and the place of obtaining the medicine was poorly reported. Similarly, information on adverse effects was poorly and vaguely reported and may be due to limited understanding among pregnant clients of causality and how to attribute cause to a particular treatment. Nursing staff at the facility were not trained in reporting of adverse drug reactions before the study onset. In our research, we used the EMA-approved product information as well as the TGA classification system for pregnancy and lactation [70], which are applicable to medicine usage in those countries but may not be aligned with the rest of the world.

One of the limitations of this analysis is the large number of tests of association that were done. In such situations false error rates increase and one may see more significant findings than there are. As these are results that were seen in a small cohort of women selected from a single health facility, further studies in a larger and more diverse population will need to be conducted to verify these findings.

The results relating to the impact of educational status on medicine use should be interpreted with caution; because the vast majority of participants (93.2%) were in the secondary level education group.

The challenges of using self-report alone have been described in other studies

The paper by van der Hoven *et al.* which used same cohort data, compared three methods of determining antenatal medicine use (self-report, clinician records and electronic pharmacy dispensing records). They concluded that using a single data collection method will under-estimate medicine use in pregnancy. Self-report appeared to be best suited to obtain a comprehensive medication history of OTC and THMs [76]. We were unable to get reliable information regarding the indications of medication used by the study subjects. for this reason this was excluded from our analysis.

5.2 Recommendations

Future studies in Sub-Saharan Africa need to employ standardized approaches to assessing medication use practices while assessing the impact of these exposures on maternal and birth outcomes. More standardised approaches are also needed to support pooling and comparison of such studies within and across regions. Such studies support the urgent need for heightened awareness among health care providers on the relationship between access to care and self-prescribing in pregnancy.

Given the high prevalence of HIV among women of child-bearing age in South Africa, there is a need to explore whether women who are treated for chronic conditions such as HIV may have different patterns of medicine use compared to women who are not being treated for such conditions. Given the risk of potentially problematic drug-drug interactions that could compromise the efficacy or increase the risk of harm associated with antiretroviral treatment, counselling and knowledge about medicine use is particularly important in this patient population.

This study demonstrates the importance of improving literacy around medicines use as part of maternal and child health services. Educational programmes that increase women's understanding of the importance of adherence to medicines such as antiretroviral therapy while minimising unnecessary or poorly considered self-medication are likely to improve the health and wellbeing both pregnant women and their children. Together with these advocacy measures, it is essential that pregnant women have affordable access to robust reproductive health services particularly family planning.

CHAPTER 6: CONCLUSION

This study provides valuable information on patterns of medication use among pregnant women living with and without HIV in Western Cape, South Africa. Medicines use was widespread in the study cohort, with a high prevalence of potentially teratogenic medicines being used during the pregnancy. Our finding highlights the urgent need for health care providers to be made aware of these practices, the importance of comprehensive medication history-taking during antenatal clinical encounters and the need for enhancing medicines safety knowledge among women and their health provider. Further research is required to determine the best approaches that can be used to improve medication literacy, reduce underreporting of medicine use, and improve medication use monitoring and recall among women of child-bearing age, particularly given that a high proportion of women may already be receiving multiple therapies before they even know that they are pregnant.

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Appendices

Appendix 1 Ethical approval

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

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

23 March 2021

HREC REF: 111/2021

Dr U Mehta
CIDER
4th Floor, Fairland House
Email: Ushma.mehta@uct.ac.za
Student: ELZZAI001@myuct.ac.za

Dear Dr Mehta

PROJECT TITLE: B POSITIVE COHORT STUDY: ASSESSING MEDICINES USE AND EXPOSURES IN PREGNANCY AND POSTPARTUM AMONG HIV-INFECTED AND HIV-UNINFECTED WOMEN IN WESTERN CAPE, SOUTH AFRICA (MASTER'S DEGREE – DR ZAINEB ELZOUKI)

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

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 March 2022.

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

The HREC acknowledge that the student: Dr Zaineb Elzouki will also be involved in this study.

Please quote the HREC REF 111/2021 in all your correspondence.

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

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

Yours sincerely

Dr AJ Hunter

HREC/REF 111/2021sb

Appendix 2 B Positive Ethical Approval (Renewal)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
26 AUG 2020
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.8.21
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	28/8/20

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)			
HREC REF Number	749/2015	Current Ethics Approval was granted until	30/08/2020
Protocol title	B positive: a population-based evaluation of expanded (anti-retroviral therapy) ART access in pregnancy		
Protocol number (if applicable)	5.0		
Are there any sub-studies linked to this study?		x Yes ☐ No	
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study		HREC REF: 541/2015 (separate FHS016 enclosed)	
Principal Investigator	Professor Andrew Boulle		

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

Department / Office Internal Mail Address	Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, 5th floor Falmouth Building, UCT FFHS, Anzio Road

1.1 Does this protocol receive US Federal funding?	x Yes	☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-enquiries@uct.ac.za)	☐ Yes	x No
If yes in 1.2 please complete section 1.3 below for invoicing purposes		
1.3 Annual Approval for **full committee** review	- R 3450 (inclusive of vat)	
For invoicing purposes, please provide:		
Sponsor's name		
Contact person		
Address		
Telephone number		
Email Address		

2. List of documentation for approval

N/A

3. Protocol status (tick ✓)

x	Open to enrolment PER
x	Closed to enrolment (tick ✓) Cohort
x	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

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

Number of participants enrolled to date	995
Number of participants enrolled, since last HREC Progress report (continuing review)	0
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	49

6. Cumulative summary of participants

Total number of participants who provided consent	995
Number of participants determined to be ineligible (i.e. after screening)	6
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	694 completed 4 postnatal visits 699 completed at least 1 postnatal visit
Number of participants withdrawn at participants' request (i.e. changed their mind)	14 not interested
Number of participants withdrawn by PI due to toxicity or adverse events	Miscarriage 19 TOP 4 Ectopic 3 Stillbirth 22 Neonatal death 9 Maternal death 6 Total: 63
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	224
224 participants did not complete all 4 postnatal visits (last visit at 12 months postnatal), mainly because they relocated out of the area. However, 699 completed at least 1 ante- and postnatal visit. The last study visit was scheduled for end of February 2020 and further retention attempts were disrupted by the SARS-CoV-2 pandemic and subsequent lockdown.	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

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

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
See attached sheet.

8. Protocol violations and exceptions (tick ✓ all that apply)

x	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☐	No prior amendments have been made since the original approval
x	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
6 maternal deaths • 1 car crash • 1 kidney failure • 3 "sick" – no further details provided • 1 unknown Unrelated to study procedures.

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	x Not applicable

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

If yes, please describe:

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	x Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	x Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	x No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
x	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

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

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	x No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	29 July 2020

Appendix 3 Maternal Medication Checklist

Confidential

Maternal Medication Use And Side Effect Table 1

PWID: _____

Visit Date _____ (DD-MM-YYYY)

Visit Code
- ○ A1
- ○ A2
- ○ A3
- ○ P1
- ○ P2
- ○ P3
- ○ P4

In what language will this be administered?
- ○ English
- ○ Xhosa

The following questions will refer to any medicines and/or remedies you have been taking. This includes ANY medicines and/or remedies from the clinic and hospital staff (doctors and nurses), the chemist, grocery stores, traditional healers, spiritual healers, friends or family members. The aim of this questionnaire is to help make a list of all the things you have taken during the past 12 months or SINCE WE LAST SPOKE TO YOU.

The following questions will refer to any medicines and/or remedies you have been taking. This includes ANY medicines and/or remedies from the clinic and hospital staff (doctors and nurses), the chemist, grocery stores, traditional healers, spiritual healers, friends or family members. The aim of this questionnaire is to help make a list of all the things you have taken SINCE WE LAST SPOKE TO YOU.

This information is important because we need to understand how the medicines and/or remedies you have been taking in the past 12 months or SINCE WE LAST SPOKE TO YOU will affect the outcome of your pregnancy.

This information is important because we need to understand how the medicines and/or remedies you have been taking SINCE WE LAST SPOKE TO YOU will affect the outcome of your pregnancy.

Please note: There is a lot of repetition to help you remember all the medications you have taken! Please bear with us and try to answer the questions as best you can.

You will be asked to list all medications you are currently taking or have previously used during the past 12 months or SINCE WE LAST SPOKE TO YOU. Please include all prescription medicines (ART, TB, and Diabetes etc.), non-prescription medicines (i.e. over the counter medicines and remedies), complementary medicines (e.g. Vitamins), traditional and/or herbal medicines and remedies.

You will be asked to list all medications you are currently taking or have previously used since we last spoke to you. Please include all prescription medicines (ART, TB, and Diabetes etc.), non-prescription medicines (i.e. over the counter medicines and remedies), complementary medicines (e.g. Vitamins), traditional and/or herbal medicines and remedies.

Table 1: SPECIFIC CONDITIONS

We are going to ask you questions about your medical history.

HIV

1. HIV?	○ Yes ○ No
1.2 When were you diagonised with HIV?	_____ (DD-MM-YYYY)
1.3 In the past 12 months OR since we last spoke to you, have you taken anything for HIV?	○ Yes ○ No
1.3 Since we last spoke to you, have you taken anything for HIV?	○ Yes ○ No
1.4 Specify medication taken for HIV?	_____
1.5 From where was the medication received? Select appropriate code	○ Doctor ○ Nurse ○ Chemist ○ Traditional Healer ○ Grocery store ○ Other
1.6 If Other, specify:	_____
1.7 Start date:	_____
1.8 Stopped or Ongoing?	○ Stopped ○ Ongoing
1.9 Stop date:	_____
1.10 What was the reason/s for stopping use? Select appropriate code	○ Felt better ○ Ran out ○ Completed course ○ Told to stop ○ Was not working ○ Side effects ○ Other reasons
1.11_1 If "told to stop" please say by whom	_____
1.11_2 If Other reasons: Specify	_____
1.12 Did you experience any side effects?	○ Yes ○ No

1.13 If YES, please specify what you took for it

_____

Tuberculosis "TB"

2.1 Tuberculosis "TB"?
- ○ Yes
- ○ No

2.2 When were you diagonised with Tuberculosis "TB"?

_____
(DD-MM-YYYY)

2.3 In the past 12 months OR since we last spoke to you, have you taken anything for Tuberculosis "TB"?
- ○ Yes
- ○ No

2.3 Since we last spoke to you, have you taken anything for Tuberculosis "TB"?
- ○ Yes
- ○ No

2.4 Specify medication taken for Tuberculosis "TB"?

_____

2.5 From where was the medication received? Select appropriate code
- ○ Doctor
- ○ Nurse
- ○ Chemist
- ○ Traditional Healer
- ○ Grocery store
- ○ Other

2.6 If Other, specify:

_____

2.7 Start date:

_____

2.8 Stopped or Ongoing?
- ○ Stopped
- ○ Ongoing

2.9 Stop date:

_____

2.10 What was the reason/s for stopping use? Select appropriate code
- ○ Felt better
- ○ Ran out
- ○ Completed course
- ○ Told to stop
- ○ Was not working
- ○ Side effects
- ○ Other reasons

2.11_1 If "told to stop" please say by whom

_____

2.11_2 If Other reasons: Specify

_____

2.12 Did you experience any side effects?
- ○ Yes
- ○ No

2.13 If YES, please specify what you took for it	_____

Sugar diabetes Type 1 or Type 2

3.1 "Sugar diabetes" Type 1 or Type 2?	○ Yes ○ No
3.2 When were you diagonised with "Sugar diabetes" Type 1 or Type 2?	_____ (DD-MM-YYYY)
3.3 In the past 12 months OR since we last spoke to you, have you taken anything for "Sugar diabetes" Type 1 or Type 2?	○ Yes ○ No
3.3 Since we last spoke to you, have you taken anything for "Sugar diabetes" Type 1 or Type 2?	○ Yes ○ No
3.4 Specify medication taken for "Sugar diabetes" Type 1 or Type 2?	_____
3.5 From where was the medication received? Select appropriate code	○ Doctor ○ Nurse ○ Chemist ○ Traditional Healer ○ Grocery store ○ Other
3.6 If Other, specify:	_____
3.7 Start date:	_____
3.8 Stopped or Ongoing?	○ Stopped ○ Ongoing
3.9 Stop date:	_____
3.10 What was the reason/s for stopping use? Select appropriate code	○ Felt better ○ Ran out ○ Completed course ○ Told to stop ○ Was not working ○ Side effects ○ Other reasons
3.11_1 If "told to stop" please say by whom	_____
3.11_2 If Other reasons: Specify	_____
3.12 Did you experience any side effects?	○ Yes ○ No

3.13 If YES, please specify what you took for it	_____

Hypertension "High Blood Pressure"

4.1 Hypertension "High Blood Pressure"?	◯ Yes ◯ No
4.2 When were you diagonised with Hypertension "High Blood Pressure"?	_____ (DD-MM-YYYY)
4.3 In the past 12 months OR since we last spoke to you, have you taken anything for Hypertension "High Blood Pressure"?	◯ Yes ◯ No
4.3 Since we last spoke to you, have you taken anything for Hypertension "High Blood Pressure"?	◯ Yes ◯ No
4.4 Specify medication taken for Hypertension "High Blood Pressure"?	_____
4.5 From where was the medication received? Select appropriate code	◯ Doctor ◯ Nurse ◯ Chemist ◯ Traditional Healer ◯ Grocery store ◯ Other
4.6 If Other, specify:	_____
4.7 Stop date:	_____
4.8 Stopped or Ongoing?	◯ Stopped ◯ Ongoing
4.9 Start date:	_____
4.10 What was the reason/s for stopping use? Select appropriate code	◯ Felt better ◯ Ran out ◯ Completed course ◯ Told to stop ◯ Was not working ◯ Side effects ◯ Other reasons
4.11_1 If "told to stop" please say by whom	_____
4.11_2 If Other reasons: Specify	_____
4.12 Did you experience any side effects?	◯ Yes ◯ No

4.13 If YES, please specify what you took for it	_____

Heart Diseases

5.1 Heart Diseases?	○ Yes ○ No
5.2 When were you diagonised with Heart Diseases?	_____ (DD-MM-YYYY)
5.3 In the past 12 months OR since we last spoke to you, have you taken anything for Heart Diseases?	○ Yes ○ No
5.3 Since we last spoke to you, have you taken anything for Heart Diseases?	○ Yes ○ No
5.4 Specify medication taken for Heart Diseases?	_____
5.5 From where was the medication received? Select appropriate code	○ Doctor ○ Nurse ○ Chemist ○ Traditional Healer ○ Grocery store ○ Other
5.6 If Other, specify:	_____
5.7 Start date:	_____
5.8 Stopped or Ongoing?	○ Stopped ○ Ongoing
5.9 Stop date:	_____
5.10 What was the reason/s for stopping use? Select appropriate code	○ Felt better ○ Ran out ○ Completed course ○ Told to stop ○ Was not working ○ Side effects ○ Other reasons
5.11_1 If "told to stop" please say by whom	_____
5.11_2 If Other reasons: Specify	_____
5.12 Did you experience any side effects?	○ Yes ○ No

5.13 If YES, please specify what you took for it	_____

Asthma

6.1 Asthma ?	◯ Yes ◯ No
6.2 When were you diagonised with Asthma ?	_____ (DD-MM-YYYY)
6.3 In the past 12 months OR since we last spoke to you, have you taken anything for Asthma ?	◯ Yes ◯ No
6.3 Since we last spoke to you, have you taken anything for Asthma ?	◯ Yes ◯ No
6.4 Specify medication taken for Asthma ?	_____
6.5 From where was the medication received? Select appropriate code	◯ Doctor ◯ Nurse ◯ Chemist ◯ Traditional Healer ◯ Grocery store ◯ Other
6.6 If Other, specify:	_____
6.7 Start date:	_____
6.8 Stopped or Ongoing?	◯ Stopped ◯ Ongoing
6.9 Stop date:	_____
6.10 What was the reason/s for stopping use? Select appropriate code	◯ Felt better ◯ Ran out ◯ Completed course ◯ Told to stop ◯ Was not working ◯ Side effects ◯ Other reasons
6.11_1 If "told to stop" please say by whom	_____
6.11_2 If Other reasons: Specify	_____
6.12 Did you experience any side effects?	◯ Yes ◯ No

6.13 If YES, please specify what you took for it

_____

Epilepsy

7.1 Epilepsy?
- ○ Yes
- ○ No

7.2 When were you diagonised with Epilepsy?

_____
(DD-MM-YYYY)

7.3 In the past 12 months OR since we last spoke to you, have you taken anything for Epilepsy?
- ○ Yes
- ○ No

7.3 Since we last spoke to you, have you taken anything for Epilepsy?
- ○ Yes
- ○ No

7.4 Specify medication taken for Epilepsy?

_____

7.5 From where was the medication received? Select appropriate code
- ○ Doctor
- ○ Nurse
- ○ Chemist
- ○ Traditional Healer
- ○ Grocery store
- ○ Other

7.6 If Other, specify:

_____

7.7 Start date:

_____

7.8 Stopped or Ongoing?
- ○ Stopped
- ○ Ongoing

7.9 Stop date:

_____

7.10 What was the reason/s for stopping use? Select appropriate code
- ○ Felt better
- ○ Ran out
- ○ Completed course
- ○ Told to stop
- ○ Was not working
- ○ Side effects
- ○ Other reasons

7.11_1 If "told to stop" please say by whom

_____

7.11_2 If Other reasons: Specify

_____

7.12 Did you experience any side effects?
- ○ Yes
- ○ No

7.13 If YES, please specify what you took for it	_____

Thyroid disease

8.1 Thyroid disease?	○ Yes ○ No
8.2 When were you diagonised with Thyroid disease?	_____ (DD-MM-YYYY)
8. 3 In the past 12 months OR since we last spoke to you, have you taken anything for Thyroid disease?	○ Yes ○ No
8. 3 Since we last spoke to you, have you taken anything for Thyroid disease?	○ Yes ○ No
8.4 Specify medication taken for Thyroid disease?	_____
8.5 From where was the medication received? Select appropriate code	○ Doctor ○ Nurse ○ Chemist ○ Traditional Healer ○ Grocery store ○ Other
8.6 If Other, specify:	_____
8.7 Start date:	_____
8.8 Stopped or Ongoing?	○ Stopped ○ Ongoing
8.9 Stop date:	_____
8.10 What was the reason/s for stopping use? Select appropriate code	○ Felt better ○ Ran out ○ Completed course ○ Told to stop ○ Was not working ○ Side effects ○ Other reasons
8.11_1 If "told to stop" please say by whom	_____
8.11_2 If Other reasons: Specify	_____
8.12 Did you experience any side effects?	○ Yes ○ No

8.13 If YES, please specify what you took for it	_____

Any psychological or mental conditions such as "thinking too much", depression, panic attacks, anxiety attacks etc. NB: Diagnosed by a doctor or nurse

9.1 Any psychological or mental conditions such as "thinking too much", depression, panic attacks, anxiety attacks etc.?	○ Yes ○ No
9.2 When were you diagonised with Any psychological or mental conditions such as "thinking too much", depression, panic attacks, anxiety attacks etc.*?	_____ (DD-MM-YYYY)
9.3 In the past 12 months OR since we last spoke to you, have you taken anything for Any psychological or mental conditions such as "thinking too much", depression, panic attacks, anxiety attacks etc.*?	○ Yes ○ No
9.3 Since we last spoke to you, have you taken anything for Any psychological or mental conditions such as "thinking too much", depression, panic attacks, anxiety attacks etc.*?	○ Yes ○ No
9.4 Specify medication taken for Any psychological or mental conditions such as "thinking too much", depression, panic attacks, anxiety attacks etc.*?	_____
9.5 From where was the medication received? Select appropriate code	○ Doctor ○ Nurse ○ Chemist ○ Traditional Healer ○ Grocery store ○ Other
9.6 If Other, specify:	_____
9.7 Start date:	_____
9.8 Stopped or Ongoing?	○ Stopped ○ Ongoing
9.9 Stop date:	_____
9.10 What was the reason/s for stopping use? Select appropriate code	○ Felt better ○ Ran out ○ Completed course ○ Told to stop ○ Was not working ○ Side effects ○ Other reasons
9.11_1 If "told to stop" please say by whom	_____

9.11_2 If Other reasons: Specify	_____
9.12 Did you experience any side effects?	○ Yes ○ No
9.13 If YES, please specify what you took for it	_____

Any other medical conditions

10.1 Any other medical conditions?	○ Yes ○ No
10.2 When were you diagonised with Any other medical conditions?	_____ (DD-MM-YYYY)
10.3 In the past 12 months OR since we last spoke to you, have you taken anything for Any other medical conditions?	○ Yes ○ No
10.3 Since we last spoke to you, have you taken anything for Any other medical conditions?	○ Yes ○ No
10.4 Specify medication taken for Any other medical conditions?	_____
10.5 From where was the medication received? Select appropriate code	○ Doctor ○ Nurse ○ Chemist ○ Traditional Healer ○ Grocery store ○ Other
10.6 If Other, specify:	_____
10.7 Start date:	_____
10.8 Stopped or Ongoing?	○ Stopped ○ Ongoing
10.9 Stop date:	_____
10.10 What was the reason/s for stopping use? Select appropriate code	○ Felt better ○ Ran out ○ Completed course ○ Told to stop ○ Was not working ○ Side effects ○ Other reasons
10.11_1 If "told to stop" please say by whom	_____

10.11_2 If Other reasons: Specify	_____
10.12 Did you experience any side effects?	○ Yes ○ No
10.13 If YES, please specify what you took for it	_____

NOTES

Please write notes and or any other comments here	_____
Interviewer completing CRF:	_____