Anaesthetists' knowledge of antiretroviral drugs with specific relevance to anaesthesia

Maryam Omar

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in the partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology

Johannesburg, 2018

Declaration

I, Maryam Omar, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

(Signature of candidate)

28th day of **September 2018** in Johannesburg.

Acknowledgements

My sincere thanks to the following people:

My family and friends for their support.

My supervisors, Helen Perrie, Professor Juan Scribante and Professor Analee Milner for their guidance and support.

The members of the Department of Anaesthesiology at the University of the Witwatersrand who participated in my study.

Abstract

Background: The inability of modern medicine to find a cure for the human immunodeficiency virus (HIV), has made the disease one of the deadliest pathogens of the 21st century. However, growing understanding of the incurable yet lethal nature of HIV has led to the development of antiretroviral treatment (ART) as a means to control the virulence of the disease and improve life expectancy. South Africa has the largest HIV epidemic in the world, with 19% of the global number of HIV cases. It also has the largest treatment programme, accounting for 20% of people on ART globally. In the perioperative context, Penfold et al estimated that 29.4% of HIV-positive patients in the state health sector will encounter surgery and anaesthesia. In view of this, healthcare professionals require knowledge of ART. This assertion is echoed by the South African Society of Anaesthesiology (SASA), which requires anaesthetists to have extensive pharmacological knowledge of ART and its interactions with anaesthetic agents. The aim of this study was to describe the level of knowledge of anaesthetists in the University of the Witwatersrand (Wits) Department of Anaesthesia on ART, with specific relevance to anaesthesia.

Method: A prospective, contextual and descriptive research design, involving a self-administered questionnaire, was used. The questionnaire consisted of two sections: demographic data and knowledge-based questions. Convenience sampling was used. The sample population included Wits anaesthetists who attended academic meetings and who voluntarily elected to participate.

Results: Descriptive statistics were used. The overall mean score obtained by the 130 participants was 8 (50%) (SD 2.8), which is 30% below the adequate score of 80%. The range of scores attained by participants was 1–15 (6–94%) with only five (4%) participants achieving a score of ≥ 80%.

Conclusion: The majority of anaesthetists in the Department of Anaesthesia did not have adequate knowledge of ART, specifically with regard to their interactions with anaesthetic agents.

List of abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
ARVs	Antiretroviral drugs
HIV	Human immunodeficiency virus
IRIS	Immune reconstitution inflammatory syndrome
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PI	Protease inhibitor
SA	South Africa
SASA	South African Society of Anaesthesiologists
VL	Viral load
WHO	World Health Organisation
Wits	University of the Witwatersrand

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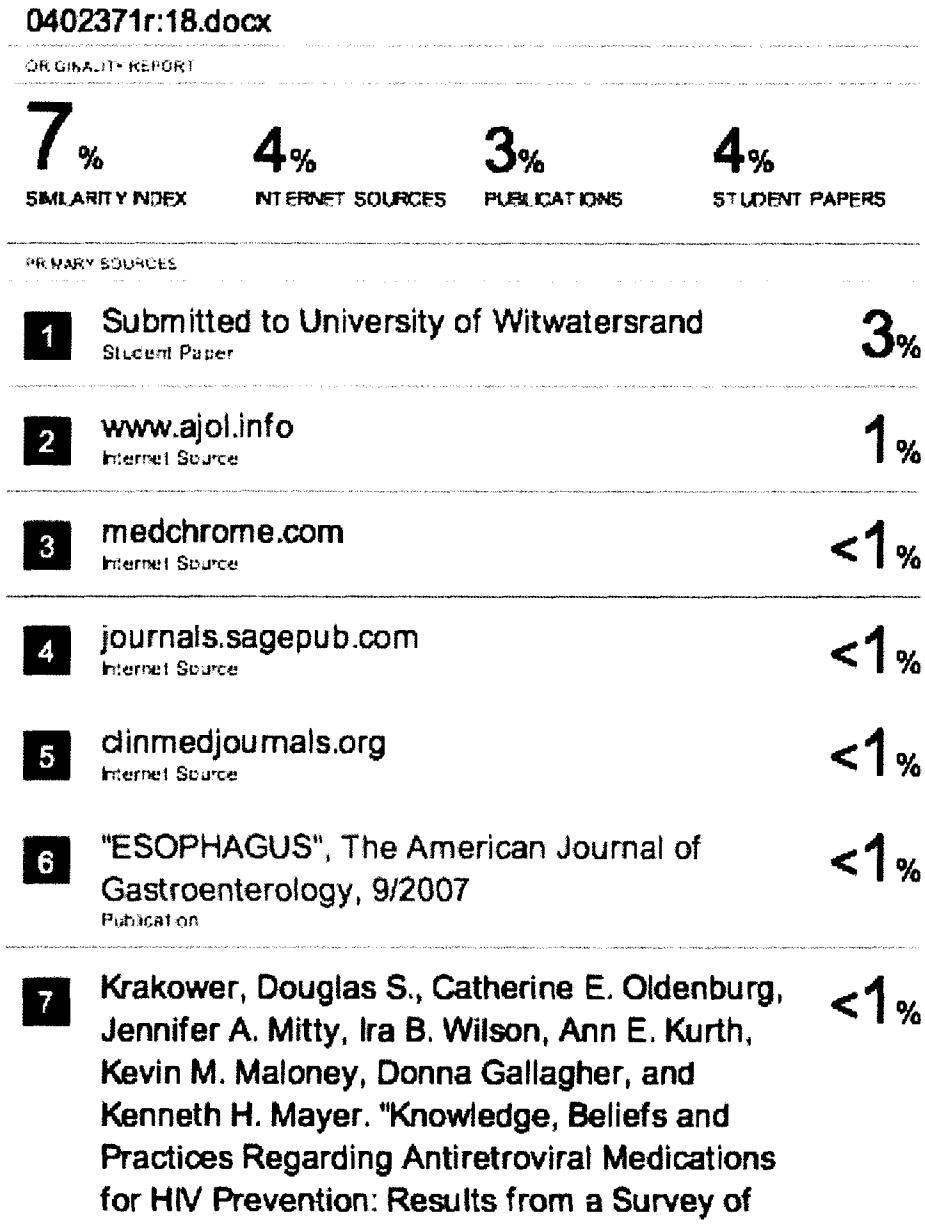

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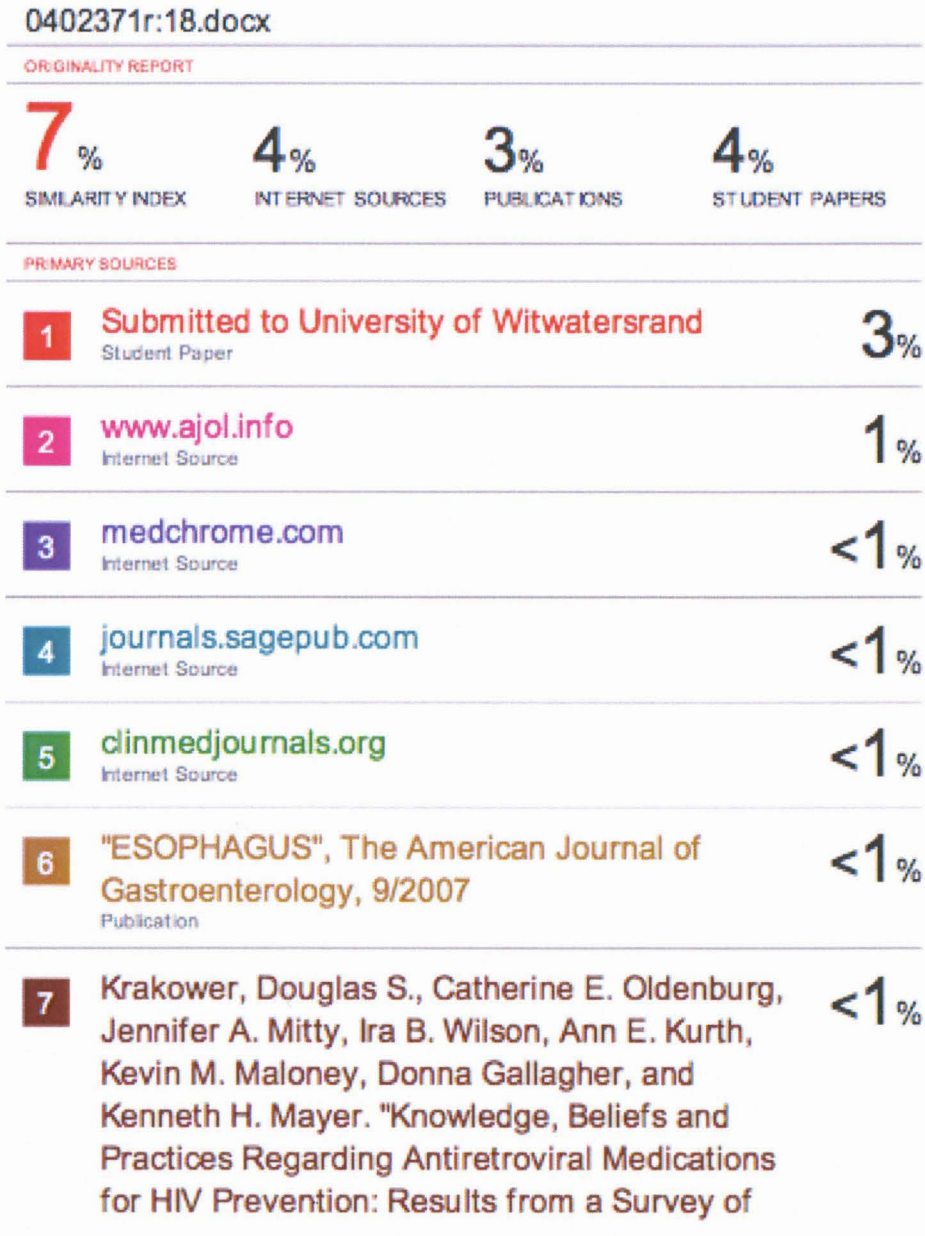

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1. Section I: Literature review

1.1 ART in South Africa

When the first cases of the human immunodeficiency virus (HIV) emerged, the disease was not entirely understood. Over time, however, it gained international attention as it evolved from an acute fatal illness to a more chronic manageable disease (1). In the 21st century, HIV has reached pandemic proportions. It is estimated that 37 million people worldwide are currently living with HIV, with two-thirds of those residing in sub-Saharan Africa (2). According to Statistics SA (2) 2016 mid-year estimates report, 13 in 100 South Africans are HIV-positive.

Internationally, South Africa (SA) has the largest ART programme (2). In 2016, it was estimated that 3.4 million HIV-positive people were on ART (3). South African health and financial policies have prioritised widespread access to ART, with an estimated annual government expenditure increase from the 2014 annual expenditure of 350 million dollars to that of 2016 at 1.5 billion dollars (1, 4). Since the introduction of ART in SA, national mortality rates have declined by 20% and life expectancy has increased (1).

The availability of ART has improved patients' quality of life and has resulted in there being more patients on ART seeking healthcare for diagnostic and therapeutic indications (5). Due to this, more HIV positive patients encounter healthcare professionals including surgeons and anaesthetists. In 2005, studies from developed countries showed that the prevalence of HIV-positive patients presenting for anaesthesia, either due to HIV related problems or other surgical problems, was 20–25% (6, 7). More recently, in 2011, a South African-based study, conducted at Chris Hani Baragwanath Academic Hospital, estimated the prevalence of the HIV positive patients exposed to anaesthesia as 29.4% (8). In view of the increasing number of HIV positive patients on ART seeking healthcare, anaesthetists should have knowledge of and insight into ART, its side effects and interactions with anaesthetic agents (9).

The goal of ART is viral suppression while strengthening the immune response as seen by a reduced viral load (VL) and increased CD4 cell count (10). It is well described that ART halts the HIV disease progression and improves both life expectancy and quality of life (11). One of the biggest obstacles to successful long-term ART programmes is the lack of adequate knowledge among patients and healthcare workers regarding ART (6).

1.2 The anaesthetists' knowledge of medication

The South African Society of Anaesthesiologists (SASA) describes the anaesthetist's scope of practice as follows: "In order to make the right decisions in accordance with the ethical and professional principles of medical practice, the doctor must have a thorough knowledge and understanding of the principles of pharmacology and possible interactions among different drugs and their effects on the health of the patient" (12). Compared to other specialists, anaesthetists self-administer drugs on a regular basis (13). During anaesthesia, a combination of several drugs is used to achieve the desired goals of hypnosis, analgesia and muscle relaxation (14).

Globally, it has been suggested that more people die from medical errors than motor vehicle accidents, breast cancer or HIV (15). A report by the Institute of Medicine highlights that deaths attributed to medication errors range between 44 000 and 98 000 (16). Perioperatively, most drug errors have been linked to human error (13). According to a survey from New Zealand, 89% of the anaesthesiologists reported a self-administered drug error (16). The practice of polypharmacy in patients with multiple illnesses perioperatively predisposes them to potentially life-threatening medication errors and interactions (16). According to the New Zealand survey, anaesthetists' risk factors for medication-related complications were found to be training and experience (4.6%), lack of senior supervision (4%) and insufficient preoperative preparation (1%) (16). Prevention of such errors has been suggested by conducting a comprehensive preoperative medication history in consultation with senior experts (16).

Anaesthetists' knowledge of pharmacology affects perioperative outcomes. One in twenty perioperative medication administration and every second operation results in a drug error (15) of which has been linked to patient harm (13). No significant difference was found between the event rates of junior doctors (5.1%), nurse anaesthetists (5.5%) and attending anaesthesiologists (4.5%) (15).

Research available regarding anaesthetists' knowledge on drugs suggests that they may lack adequate knowledge of certain drugs (16), despite the fact that they are considered to be experts on the pharmacology of anaesthetic agents and resuscitation drugs (12). In the event of an on table cardiac arrest in the operating theatre, the anaesthetist would be expected to initiate the resuscitation of the patient. This requires thorough knowledge of the resuscitation algorithm, drugs administered, correct dosages and pharmacology (16).

Adrenaline is one of the emergency drugs used by anaesthetists to deal with various life-threatening complications. A South African study showed that anaesthetists' overall knowledge of the drug adrenaline was poor. Specific domains they lacked knowledge in were cardiac arrest and anaphylaxis, where the pass rate was 46% and 14% respectively. Adrenaline doses is another aspect that anaesthetists lacked knowledge on, with 86% not knowing the intravenous bolus dose of adrenaline and a similar percentage not knowing the doses for an adrenaline infusion (40).

A study carried out in the United Kingdom (UK) in 2005 surveyed 150 anaesthetists from five different hospitals, revealing a lack of knowledge among anaesthetists in conducting a resuscitation in an adult. In the three years preceding the study, 33% of anaesthetists had received formal advanced life support training, while 41% had received no formal training. It was also found that both groups lacked knowledge of the UK resuscitation algorithm. Of those anaesthetists who received no training, 82% knew the initial defibrillation dose and 88% knew the correct dose of adrenaline. Comparably, in trained anaesthetists, 87% knew the initial defibrillation dose and 91% knew the correct dose of adrenaline.

Similarly, in 1995, Bell et al (19) assessed the basic and advanced cardiopulmonary resuscitation skills of 30 anaesthetists. The study found inadequate knowledge regarding drug dosage selection (77%), adrenaline dose and (46%) atropine dose (19). Moreover, the management of ventricular fibrillation 8 (27%) and asystole was carried out correctly by 30% of anaesthetists (19). Errors during CPR included the incorrect use of drugs such as sodium bicarbonate and calcium (19).

In 2012, another UK-based study revealed that doctors displayed a deficit in knowledge of adrenaline guidelines in anaphylaxis, with a mere 41 (14.4%) out of 284 doctors administering adrenaline according to the guidelines (20). In addition, a 2004 Australian-based study assessed the resuscitation of newborns and revealed that only eight of the 32 anaesthetists felt confident in their ability to conduct a successful resuscitation on newborns (20).

A study conducted in Denmark, in 2011, revealed limited knowledge among anaesthesiologists on intralipid rescue of local anaesthetic systemic toxicity (21). Local anaesthetic drugs are used in daily practice and systemic toxicity is a well-described life-threatening complication. Telephonic surveys of 34 hospitals with attending anaesthesiologists were included; subsequently 76% of respondents were found to be unable to provide lipid rescue therapy because the attending anaesthesiologist had no knowledge of the treatment. Twenty-two (65%) of the anaesthesiologists were aware of the use of the intralipid emulsion in the management of local anaesthetic toxicity, but only 24% had access to local guidelines on lipid rescue therapy, while the same eight (24%) anaesthesiologists knew where to find the emulsion (21).

1.3 Anaesthetists' knowledge of ART

The researcher did not identify literature on anaesthetists' knowledge of ART with specific relevance to anaesthesia, as the literature available on the subject demonstrated the knowledge of other healthcare workers including nurses, doctors, midwives, infectious disease specialists and laboratory workers.

1.3.1 ART knowledge among healthcare workers

This discussion will describe healthcare workers' knowledge on ART, beginning with the literature from South Africa, moving on to the African continent as a whole, and then beyond to America, the UK, France and New Zealand.

A South African study conducted in 2011 looked at the ART programme at two healthcare facilities (Kimberly Hospital Complex and Galetshewe Day Hospital) in the Northern Cape (22). The focus was to assess the knowledge of both patients and staff regarding ART and its side effects. The staff included consisted of nurses, pharmacists and pharmacist assistants. Data showed that 100% of the staff displayed adequate knowledge of side effects (22). Overall, this study highlighted that clinic staff displayed adequate knowledge regarding ART side effects, adherence and impact. The study subsequently suggested that difficulties in patient–staff communication contributed to inadequate patient education.

A study conducted in KwaZulu-Natal, which is considered to be the epicentre of the epidemic with an HIV prevalence of 38.7%, assessed private sector doctors' management of HIV patients and their treatment (23). Of the 235 doctors who participated in the study, 105 (78.9%) reported that they thought they had adequate knowledge on ART. Of the 38 doctors who were unwilling to manage HIV patients, 80% reported lack of knowledge as their reason (23). No mean knowledge score was quantified.

A Nigerian study conducted in 2008 assessed the knowledge of 426 healthcare professionals, aged 19 to 60 years, which included nurses, doctors and laboratory workers (24). Of these participants, 46% obtained a score of 50%. The researcher in the study does not define adequate knowledge, however they classify the 50% score as "fair knowledge". Surveys took place in two phases, assessing healthcare professionals' knowledge of HIV and treatment. Factors influencing knowledge were age, professional designation, medical talks, and contact with HIV patients. Knowledge scores differed among professional designations with doctors scoring highest, followed by nurses, and then laboratory workers. Knowledge was also found to be a function of age; as age increased, knowledge decreased. The study

suggests the reason for this is that the older participants lacked knowledge of HIV because they were not taught about the virus during their school careers, whereas the younger participants have lived in the HIV era where school curricula focus on HIV education (24).

A study conducted by the Infectious Diseases Institute in Uganda in 2009 assessed the knowledge base and training needs at 44 health facilities among 265 health professionals, of whom 64% were clinical officers, nurses and midwives, and 36% were doctors (25). The researchers' intentions were to highlight how adequate knowledge on ART is imperative for the prescribing clinicians. The researcher did not define adequate knowledge as a numerical score, but merely stated that higher scores were considered to be adequate knowledge. Seven per cent of doctors, 42% of clinical officers, 35% of nurses and 77% of midwives assessed their overall knowledge as adequate (25).

A study based in Cameroon in 2007 (26), conducted in 27 hospitals, assessed HIV physicians' knowledge on ART at three levels of healthcare (central, provincial and district) (26). A knowledge questionnaire was completed by 93 physicians, where each questionnaire was scored out of 27 and "higher values denoted better knowledge" (26). While knowledge was good regarding the awareness of the criteria for the initiation of ART (80% correctly answered), there was a uniformly poor score noted in knowledge of the management of specific subpopulations such as paediatrics (26). Eighty per cent of physicians were general practitioners. Seventy-five per cent of physicians had benefited from at least one training programme in HIV care, while 47% had at least three years of experience in this regard. Mean knowledge score was 21.3 (SD ±4.8) (26). More than 50% of physicians had a score above 23. Factors associated with better knowledge included training in ART, collaboration with other healthcare practitioners and establishing relationships with patients (26).

A study conducted in Cote d'Ivoire in 2003 used self-administered questionnaires and subsequently found that physicians who had more experience in the care of HIV-positive patients were more knowledgeable. Twenty one of the 88 questions assessed knowledge on HIV, ART and their side effects. One hundred and twenty-

three respondents from six centres took part, and of these respondents, 45.1% had taken care of more than 20 HIV positive patients in the previous year. Physician experience was found to be proportional to knowledge, qualifications and the number of HIV patients under their care (27).

In 2007, a survey conducted at the Johns Hopkins Medical Centre in Baltimore explored the extent of ART knowledge among physicians (28). The findings revealed that those with more specialised training in HIV medicine and those with more extensive experience had more insight and knowledge about the pharmacology of ART. Infectious disease specialist physicians whose practices had a high turnover of outpatients showed more extensive ART knowledge as compared to residents and attending physicians who were not infectious disease specialists and who managed fewer outpatient numbers (28).

A study conducted at Harvard Medical School in 2009 assessed physicians' knowledge on HIV and ART (29). On average, physicians were correct on 8.2 (75%) of the 11 questions on the HIV knowledge scale. Better knowledge scores were found amongst specialists in infectious diseases (29).

A study conducted in Brazil in 2002 investigated barriers to ARV adherence. The study described physician–patient communication as a powerful determining factor for ART adherence (30). Inadequate knowledge was subsequently identified as a barrier to adherence, and patients who experienced adverse effects were less likely to adhere (30). Of the 40 physicians interviewed, 47.5% had specialised training in HIV and ART. Physicians were apprehensive about educating patients on their ART side effects, as they feared that if patients understood the potential side effects they would not commence the treatment at all (30).

A review conducted in 2006 assessed doctors' barriers to HIV care and treatment. One of the barriers identified was inadequate knowledge and training regarding ART among physicians and doctors (31). Furthermore, doctors with better knowledge were found to be more experienced in treating large numbers of HIV-positive patients on ART (31).

A study conducted in 2013 in New England, among healthcare workers in a regional AIDS Education and Training Centre, involved an online survey that assessed participants' knowledge regarding ART. Participants included nurse practitioners (24%), primary care physicians (22%), and infectious diseases specialists (21%). Of the 105 ART prescribing clinicians who participated, 64% were knowledgeable on ART, its side effects and potential for treatment resistance (27).

1.3.2 ART knowledge among patients

The research problem does not focus on patients' knowledge, but rather on anaesthetists' knowledge. However, it is interesting to note that the literature suggests that there is a direct link between doctors' and patients' knowledge of ART and the degree of patient adherence. A study by Herbert et al (22) investigating non-adherence behaviours, showed that patients who defaulted on treatment lacked certain knowledge about ART. The literature highlighted the need for extensive patient and healthcare professional-based education and communication to alleviate stigma and improve education (22).

1.4 Antiretroviral drugs

This study includes an overview of ARVs to outline the different classes available, the mechanisms of action and the side-effect profiles. There is a vast amount of literature available on ARVs alone; however, for the purpose of this research topic, the focus will be limited to the relevance to anaesthesia. For ease of understanding, the relevant literature has been summarised and tabulated.

1.4.1 Classification of antiretroviral drugs

Healthcare professionals are required to have a working knowledge of many ARVs, including their interactions with other drugs. For the purpose of this review, the focus will be restricted to the current South African HIV Clinicians Society guidelines and the commonly prescribed ARVs. Table 1.1 lists the classes of ARVs.

Table 1.1 Classes of ARVs adapted from Milner & Welsch (9)

ARV	Example of drugs
Nucleoside reverse transcriptase inhibitors (NRTIs)	zidovudine, lamivudine, emtricitabine, stavudine, didanosine, abacavir, tenofovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	nevirapine, efavirenz, etravirine, delavirdine
Protease inhibitors (PI)	ritonavir, indinavir, saquinavir, lopinavir
Fusion inhibitors	enfuvirtide
Integrase inhibitors	raltegravir, elvitegravir
Chemokine co-receptor antagonists	maraviroc

Figure 1 presents a pictorial description of a CD4 cell and the HIV replication within the cell. The overall effect of ARVs is the suppression of HIV replication, inflammation reduction, immune activation and the gradual restoration of CD4 cell numbers. According to a numbered key, each class of ARVs is classified according to its effect and mechanism of action (55). Table 1.1 provides an explanation of a mechanism of action for each class of ARV depicted in the Figure 1.

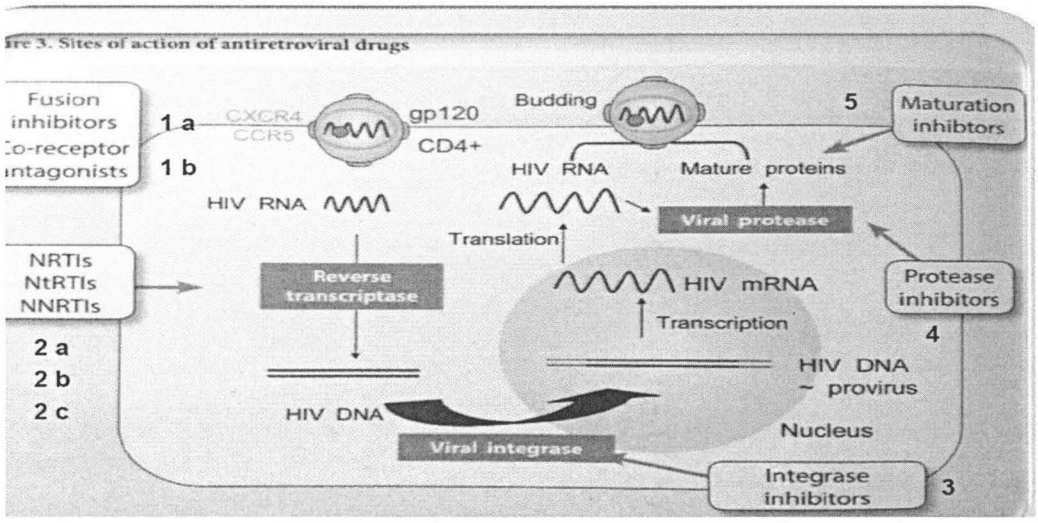

Figure 1 Mechanism of action of ARVs

Source: Adapted from Milner and Welsch (9)

Key:

1a Fusion inhibitors

1b Co-receptor antagonists

2a Nucleoside reverse transcriptase inhibitors

2b Nucleotide reverse transcriptase inhibitors

2c Non-nucleoside reverse transcriptase inhibitors

3 Integrase inhibitors

4 Protease inhibitors

5 Maturation inhibitors

1.4.2 Drug interactions

"The potential for drug interactions is probably greater in anaesthesia than in other areas of medicine" (32). When the effect of one drug is influenced by the simultaneous administration of another, a drug interaction has occurred. These interactions can be harmful depending on the properties of each drug administered. It has been estimated that HIV positive patients receive up to nine prescription medications during the course of their disease (32). Anaesthetists use a variety of drugs of different classes, each with their own pharmacokinetic and pharmacodynamics profile. Patients on ART are often on multiple other drugs as well. Perioperatively anaesthetists administer several drugs per patient and in the

setting of multiple drugs simultaneously administered, there is a greater risk of adverse drug interactions (32).

The mechanisms involved in drug interactions are summarised in Table 2 and may be one of three types: pharmaceutical, pharmacokinetic, or pharmacodynamics (32). NNRTIs and PIs are the drugs most implicated in drug interactions (33) and their overall effect on anaesthetic agents is via hepatic enzyme induction and/or inhibition (34). Owing to the interindividual variability of pharmacogenomics, interactions vary from patient to patient (35) It is therefore suggested that the anaesthetist avoid these agents where possible; however, if needs be, careful calculation and titration of safe doses may benefit the patient (36).

Table 1.2 Summary of the principles of drug interactions

Type of reaction	Interaction between anaesthetic agents and ARVs
Pharmaceutical: Precipitation of a chemical reaction as a result of physical property interacting with a drug.	Not relevant to ARVs as anaesthetists do not administer ARVs intraoperatively; for example, photosensitivity reaction where exposure of a drug to light causes breakdown of the drug.
Pharmacokinetic: Body's effect on the drug: Absorption	Absorption of ARVs may be reduced due to the opioids' effects of delayed gastric emptying, nausea and vomiting (35). The absorption of maraviroc may be increased by alfentanil, fentanyl and midazolam, which all inhibit the P glycoprotein transporter (35).
Distribution	Protein binding: NRTIs poorly protein bound; NNRTIs and PIs highly protein bound. Drug plasma levels are altered in altered protein states and therefore dose adjustments may be necessary
Metabolism • Inducers • Inhibitors	Maraviroc is metabolised by the CYP3A4 enzyme, but there is no evidence to suggest it affects the pharmacokinetics of other substrates of this coenzyme such as midazolam (37). Inducers catalyse enzyme activity, increase metabolism of the parent drug and levels of metabolites, result of the parent drug. Nevirapine is known for its ability to induce its own metabolism, requiring doubling of the dose. Due to its ability to induce hepatic enzymes, it may result in lowering the levels of other agents, which share its metabolic pathway, for example fentanyl, rifabutin, rifampicin, midazolam, oral contraceptive pill and protease inhibitors (38). Inhibitors depress hepatic enzyme activity, resulting in increased parent drug levels with the potential for prolonged duration of action and/or effects from toxic levels. Protease inhibitors like ritonavir are commonly implicated in the inhibition of cytochrome p450 enzymes, resulting in increased levels of several drugs: pethidine, calcium channel blockers, midazolam, neuromuscular blocking agents and fentanyl (34). The enzyme inhibition precipitates the toxic effects of these parent drugs, e.g. excessive sedation, delayed awakening, refractory hypotension, nausea, vomiting and seizures (5)
Excretion	ARVs that are renally excreted (NRTIs) require dose adjustment in renal impairment. Tenofovir is nephrotoxic, therefore concurrent use of nephrotoxic agents should be avoided and dose adjustments to renally excreted anaesthetic agents may be necessary.
Pharmacodynamic : Drug's effect on the body (30) • Additive • Synergistic	May be avoided by careful selection of anaesthetic agents that have minimal effects on hepatic or renal systems. NRTIs implicated in causing lactic acidosis of which 2–9% of patients on ARVs are symptomatic, hence long-term propofol infusions

• Antagonistic	should be avoided in such patients (39).

1.5 Drugs preferred by anaesthetists

As outlined in Table 1.3, certain anaesthetic agents do not interact with ARVs and are preferred by anaesthetists when managing patients on ARVs. These agents have metabolic pathways independent of the hepatic cytochrome p450 isoenzymes, especially CYP3A4 (34)

Table 1.3 Interactions between ARVs and anaesthetic agents, and preferred drugs by anaesthetists

Agent	Interactions with ARVs and the effects thereof	Preferred drug by anaesthetist
General anaesthetics Intravenous	Propofol may have an inhibitory effect on macrophage, monocyte and natural killer cell function. NRTIs cause mitochondrial toxicity, which raises concerns regarding the recurrent use of propofol infusions (40). Etomidate's use has been cautioned due to adrenal axis suppression. Immunosuppression may be triggered as early as 15 minutes post induction and may persist for 3 to 11 days (41).	Propofol
Inhalational	Desflurane may be the preferred volatile due to its independence of the CYP450 metabolic pathway, as only 0.2% is metabolised (38). The data is inconclusive regarding the safety of nitrous oxide and ARVs.	Desflurane, Sevoflurane, Isoflurane
Analgesics Opioids	Experimental data suggest opioids detrimental to immune system (36). Inconclusive data to support avoidance (5). Due to common metabolism with Nevirapine via CYP3A4, Fentanyl may either be potentiated or inhibited (14). Ritonavir decreases fentanyl clearance by 70%, causing respiratory depression with small doses. Plasma pethidine levels	Sufentanil, Morphine, Remifentanil

	decreased due to increased hepatic metabolism of pethidine and its metabolite norpethidine, which may cause seizures (7).	
Muscle relaxants Depolarising Non-depolarising	Case studies reported on prolongation of neuromuscular blockade in patients on ART (33). The underlying mechanism is not entirely understood, is suggested to be due to the HIV infection itself, HIV-associated hepatic dysfunction, myopathy, or the polypharmacy of ART (42) Suxamethonium use in patients on ART with myopathy/neuropathy potentially lethal hyperkalaemic cardiac arrest. Data is inconclusive, no clear contraindication to suxamethonium has been suggested (5). Benzylisoquinolones: e.g. atracurium and cis-atracurium independent of interactions. Aminosteroids: vecuronium/rocuronium lack of conclusive evidence of interactions.	Atracurium, cisatracurium
Benzodiazepines	Increased susceptibility to midazolam's sedative and respiratory depressant effects. Ritonavir and saquinavir (34) increase the bioavailability of oral benzodiazepines from 41 to 90% by inhibiting metabolism (21). Nevirapine is broken down by and induces CYP3A4 and CYP2B6 and thus decreases midazolam plasma concentration.	Lorazepam, Temazepam
Miscellaneous Ergot alkaloids Proton pump inhibitors Statins	With Efavirenz prolonged vasospasm occurs Proton pump inhibitors will increase PI plasma concentrations. PIs and statins should not be given together (38)	

1.6 Adverse effects

ARVs have systemic adverse effects. These effects have been categorised into two groups, namely, acute life-threatening complications and chronic complications (11).

1.6.1 Acute life-threatening complications

As the perioperative physician, the anaesthetist should have an understanding of these complications. The literature suggests that healthcare workers, such as nurses and doctors, have inadequate knowledge levels regarding ARV-related complications, however no literature was identified that describes the extent of anaesthetists' knowledge of these complications. These complications will be briefly discussed here.

Lactic acidosis

Lactic acidosis is an uncommon complication attributed to the use of NRTIs and results from mitochondrial toxicity (5). Clinically, it presents as a syndrome with a broad constellation of signs and symptoms ranging from asymptomatic laboratory diagnosed hyperlactaemia or lactic acidemia, to a more severe state of lactic acidosis and then to life-threatening fulminant multi-organ failure (43). Lactic acidosis usually presents in adults within nine months of commencement of NRTI therapy and is uncommonly seen in long-term therapy over two years.

It is important for the anaesthetist to be aware of the risk factors associated with the development of this complication, namely, patients on NRTIs (especially stavudine and didanosine), black race, pregnant females, overweight patients, recent rapid weight gain or loss and the presence of underlying liver disease (11). The symptoms are non-specific nausea, vomiting, fatigue, weight loss and abdominal pain. The associated mortality is up to 77%; therefore, anaesthetists should be fully aware of appropriate management for this complication. The perioperative recommendations in the scenario of suspected lactic acidosis

include stopping the NRTIs, instituting supportive care and, if elective surgery is required, postponing the procedure until the lactic acidosis resolves (38).

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an acute exacerbation of inflammatory disorders and is described as a systemic pro-inflammatory state (5) that may develop seven days to four weeks following the initiation of ART (44). Clinical signs and symptoms, for example latent and opportunistic infections, appear to worsen despite an improvement in the immune status (44). Chronic diseases such as sarcoidosis and rheumatic diseases may transiently deteriorate after ART commencement (43). The incidence of patients starting ART who develop IRIS ranges from 10 to 50% (45). Research has shown that 22% of ART related deaths are attributable to IRIS (45).

1.6.2 Long-term chronic complications

The long-term complications associated with ART are due to drug induced secondary organ changes (32). These adverse effects, illustrated in Table 1.4, have been shown to have a negative impact on adherence (32). Lack of adherence is associated with drug resistance and treatment failure. It has been found that between 90 and 95% ART adherence is required to prevent the potential development of treatment resistance (54). The vast spectrums of chronic complications are of concern to anaesthetists, as these systemic effects have an influence on the entire perioperative anaesthetic plan and prognosis (5).

Table 1.4 Summary of systemic complications associated with ART

System affected	Specific effects	Causative ARV	Anaesthetic implications
Neurological	HIV associated dementia Chronic pain (2, 10) Peripheral neuropathy	Stavudine Didanosine	Consent Multimodal analgesia Cautious with regionals
Musculoskeletal	Osteoporosis, osteopenia (10) Pathological fracture, impaired vitamin D activation	PIs	Positioning in anaesthesia
Haematological	Bone marrow suppression (9, 32)	Zidovudine	Pre-op full blood count Transfusion triggers
Endocrine	Insulin resistance Lipodystrophy (32)	PIs	Glucose monitoring Potential difficult airway
Cardiac	Arrhythmias (32	PIs (10)	ECG, Echo
Respiratory	PTB, PCP, Atypical pneumonia (10)		CXR, ABG Post-op pulmonary complications
Vascular	Hyperlipidaemia (10, 32) Endothelial dysfunction	PIs	Risk stratification for vascular pathology
Urogenital	Reduced GFR, AKI (10) Tubular dysfunction (11)	Tenofovir	Pre-op renal function tests Avoid nephrotoxic agents
Hepatobiliary	Hepatotoxicity (46) Hepatic failure	NNRTIs	Pre-op liver function tests Cautious dosing (5)
Gastrointestinal	Nausea, vomiting (32)	NNRTIs, NRTIs	Aspiration risk, altered absorption Electrolyte imbalances, dehydration (36)

1.7 Perioperative management and treatment protocols

1.7.1 Perioperative anaesthetic management

The researcher was not able to identify literature on anaesthetists' knowledge of perioperative management regarding ART interruption. Perioperatively, the interruption of ART occurs due to various patient, drug and anaesthetic-related factors. A study on ART treatment interruption has demonstrated the benefits of continuous treatment versus the disadvantages of interrupted treatment. Inconclusive data regarding the outcomes of structured ART interruptions has been unable to identify any beneficial effect of perioperative treatment interruption (23). Treatment interruption has been associated with a transient viral load rebound and decreased CD4 counts, which may result in treatment failure (47).

The literature suggests that ART interruption can predispose the patient to the development of opportunistic infections, malignancies, the progression of the HIV disease and the potential for the development of a drug-resistant viral strain (5). Perioperatively, the administration of NNRTI should be altered. If abrupt termination of the drug occurs in the starvation period, the viral replication persists and the lingering presence of the drug at sub-therapeutic plasma levels for this prolonged time provides the platform for the development of NNRTI resistance. It is recommended that the NNRTI should be discontinued and changed to a dual NRTI regimen one to two weeks prior to surgery. For anticipated ileus it is suggested to discontinue the NNRTI regimen for one to two weeks prior to surgery and to change to a dual NRTI regimen. Subcutaneous, intravenous, gastric/jejunal and gastrostomy feeding tubes are described as alternative routes of ART administration perioperatively to reduce sub-therapeutic levels and potential treatment failure and the development of resistance (5).

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2. Section II: Journal guideline for authors

This section includes the author guidelines that the researcher followed with regard to formatting the article. These are then followed in the draft article. The journal to which this article is intended to be submitted is the *Southern African Journal of Anaesthesia and Analgesia.*

The formatting of this research report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the rest of the research report in order to comply with the author guidelines for the journal to which it is intended to be submitted.

Southern African Journal of Anaesthesia and Analgesia author guidelines

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The *SA Journal of Anaesthesia and Analgesia* aims to publish original research and review articles of relevance and interest to the anaesthetist in academia, public sector and private practice. Papers are peer reviewed to ensure that the contents are understandable, valid, important, interesting and enjoyed. All manuscripts must be submitted online.

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The following contributions are accepted (word counts exclude abstracts, tables and references):

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* **Drug Reviews** (2400 words/ 3-4 pages)
* **Case Studies** (1800 words/ 3 pages)
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Please see the journal's section policies section policies for further details.

FULL AUTHOR GUIDELINES

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All articles must have a title page with the following information and in this particular order: Title of the article; surname, initials, qualifications and affiliation of each author; The name, postal address, e-mail address and telephonic contact details of the corresponding author and at least 5 keywords.

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All articles should include an abstract. The structured abstract for an Original Research article should be between 200 and 230 words and should consist of four paragraphs labelled Background, Methods, Results, and Conclusions. It should briefly describe the problem or issue being addressed in the study, how the study was performed, the major results, and what the authors conclude from these results. The abstracts for other types of articles should be no longer than 230 words and need not follow the structured abstract format.

Keywords

All articles should include keywords. Up to five words or short phrases should be used. Use terms from the Medical Subject Headings (MeSH) of Index Medicus when available and appropriate. Key words are used to index the article and may be published with the abstract.

Acknowledgements

In a separate section, acknowledge any financial support received or possible conflict of interest. This section may also be used to acknowledge substantial contributions to the research or preparation of the manuscript made by persons other than the authors.

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Cite references in numerical order in the text, in superscript format (Format> Font> Click superscript). Please do not use brackets or do not use the foot note function of MS Word.

In the References section, references must be typed double-spaced and numbered consecutively in the order in which they are cited, not alphabetically.

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1. Jun BC, Song SW, Park CS, Lee DH, Cho KJ, Cho JH. The analysis of maxillary sinus aeration according to aging process: volume assessment by 3-dimensional reconstruction by high-resolutional CT scanning. Otolaryngol Head Neck Surg. 2005 Mar;132(3):429-34.
2. 2. Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.

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The Editor, SAJAA, E-mail: toc@sajaa.co.za

Note: Ensure that the article ID [reference] number is included in the subject of your email correspondence.

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1. Please consult the "Uniform requirements for manuscripts submitted to biomedical journals" at www.icmje.org

2. Please consult the guide on Vancouver referencing methods at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=citmed.TOC&depth=2
3. The submission must be in UK English, typed in Microsoft Word or RTF with no double spaces after the full stops, double paragraph spacing, font size 10 and font type: Times New Roman.
4. All author details (Full names, Qualifications and affiliation) must be provided.
5. The full contact details of corresponding author (Tel, fax, e-mail, postal address) must be on the manuscript.
6. There must be an abstract and keywords.
7. References must strictly be in Vancouver format. (Reference numbers must be strictly numerical and be typed in superscript, not be in brackets and must be placed AFTER the full stop or comma.)
8. It must be clear where every figure and table should be placed in the text. If possible, tables and figures must be placed in the text where appropriate. If too large or impractical, they may be featured at the end of the manuscript or uploaded as separate supplementary files.
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11. Figure numbers: Arabic, table numbers: Roman

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As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. This manuscript has currently only been submitted to SAJAA and has not been published previously.
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4. The submitting/corresponding author is duly authorised to herewith assign copyright to the South African Society of Anaesthesiologists (SASA).
5. All co-authors have made significant contributions to the manuscript to qualify as co-authors.
6. Ethics committee approval has been obtained for original studies and is clearly stated in the methodology.
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South Afr J Anaesth Analg: ISSN (Print): 2220-1181, ISSN (Web): 2220-1173

3. Section III: Article

Anaesthetists' knowledge of antiretroviral drugs with specific relevance to anaesthesia

Maryam Omar (MBChB, DA (SA))

Helen Perrie (MSc)

Juan Scribante (M Cur)

Analee Milner (MBBCh MPharm Med FFA(SA) FRCP(C))

Department of Anaesthesiology, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Corresponding author

Maryam Omar (MBChB, DA(SA))

Department of Anaesthesiology

26 Chris Hani Road

Johannesburg, 1864

South Africa

E-mail: maryamomar3@gmail.com

Tel: 011 933 0000

Keywords: anaesthetists' knowledge, antiretroviral therapy, drug interactions, perioperative antiretroviral management

Abstract

Background: Modern medicine's inability to find a cure for the human immunodeficiency virus (HIV), has made the virus a deadly pathogen of the 21st century. The growing understanding of the incurable nature of HIV has led to the development of antiretroviral treatment (ART) as a means to control the virulence of the disease and improve life expectancy. South Africa has the largest HIV epidemic in the world, with 19% of the global number of HIV cases. It also has the largest treatment programme, accounting for 20% of people on ART globally. It has been estimated that 20 to 25% of HIV-positive patients will encounter surgery and anaesthesia. In view of this, healthcare professionals require knowledge of ART. These sentiments are echoed by the South African Society of Anaesthesiology, which requires anaesthetists to have extensive pharmacological knowledge of ART and interactions with anaesthetic agents. The aim of this study was to describe the level of knowledge of anaesthetists at the University of the Witwatersrand Department of Anaesthesiology on ART, with specific relevance to anaesthesia.

Method: A prospective, contextual and descriptive research design, utilising a self-administered questionnaire, was used. The questionnaire consisted of two sections: demographic data and knowledge-based questions. Convenience sampling was used. The sample population included anaesthetists who attended academic meetings and who voluntarily elected to participate. Descriptive and inferential statistics were used to analyse the data.

Results: The overall mean score obtained by the 130 participants was 50% (SD 18%), which is 30% below the adequate score of 80%. The range of scores attained by participants was 6 to 94% with only 4% of the participants achieving a score of $\geq$ 80%.

Conclusion: The majority of anaesthetists in the Department of Anaesthesiology did not have adequate knowledge of ART, specifically with regard to interactions with anaesthetic agents.

Introduction

According to Nelson Mandela, "HIV/AIDS is the greatest danger we have faced for many, many centuries. HIV/AIDS is worse than a war. It is like a world war. Millions of people are dying from it".[1]

As the disease has evolved into a global pandemic, HIV/AIDS burdens the health and economic sectors across all continents.[2] Africa has been identified as the epicentre of the epidemic.[3] South Africa was estimated to have approximately seven million people living with HIV in 2016,[3] with estimates of new infections and AIDS related deaths at 11% and 16% respectively.[4] According to the World Health Organisation, the actual worldwide population on antiretroviral treatment (ART) as of 2016 was estimated to be 19 million people[5] 19% of whom are in South Africa.[3] With the advent of ART over the past two decades, life expectancy has increased in HIV positive patients.[4] Therefore, with the exponential expansion of HIV and the ART induced patient longevity, healthcare professionals will commonly encounter patients on ART.[6]

Anaesthetists act as the advocate for the anaesthetised patient.[7] Since the anaesthetist plays an important role in the course of the perioperative plan to each patient, the HIV-positive patient on ART will also require this individualised care.[8, 9] According to estimates, 20 to 25% of HIV-positive patients require surgery in their lifetime, hence it is essential that anaesthetists are knowledgeable about ART.[9-13]

ART includes combination regimens of at least three drugs from different classes, which have the aim of suppressing the viral replication whilst retarding the disease progression to ultimately improve quality of life.[6] In South Africa, ART entails specific combinations of drugs: either one or two nucleoside reverse transcriptase inhibitors (NRTIs), plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), and/or one protease inhibitor (PI). These NRTIs, NNRTIs and PIs are categorised according to common pharmacokinetic and pharmacodynamic profiles. This knowledge is imperative for anaesthetists, as each of these classes interacts individually with specific anaesthetic drugs, for example NNRTIs and opioids, PIs and benzodiazepines, and NRTIs and antibiotics.[6, 9, 13] These interactions are complex and affect the dosing and toxicity of a large spectrum of anaesthetic drugs and, consequently, the perioperative outcomes.[6]

In addition to other adverse effects, all ART is associated with acute life-threatening effects as well as chronic lifelong complications.[6] The commonly known acute life-threatening complications associated with ART are lactic acidosis, immune reconstitution inflammatory syndrome, hepatotoxicity and nephrotoxicity, all of which significantly affect the anaesthetist's perioperative plan[6]. Chronic complications commonly associated with ART manifest in all body systems. Thus, the anaesthetist needs to be aware of these acute and chronic complications in order to apply appropriate and holistic anaesthetic techniques and perioperative management.[8]

Because of the perioperative starvation guidelines, patients often omit their routine medications, including ART.[6] Clinical trials have shown that interruptions of continuous ART can exacerbate long-term morbidity and mortality among such individuals,[14] as interruptions result in the rapid development of drug resistant strains, as well as the development of opportunistic infections and malignancies.[6] The anaesthetist's awareness of the impact of treatment interruption is imperative for the long-term outcome of the patient.[6]

Currently the knowledge of anaesthetists with regards to ART is not known. In this study, the ART knowledge of anaesthetists in the University of the Witwatersrand Department of Anaesthesiology is investigated, with specific relevance to anaesthesia.

Methodology

A prospective, contextual, descriptive research design was applied. Approval from the Human Research Ethics Committee (Medical) and appropriate authorities was obtained. The sample size was realised by the number of responses received. A response rate of 60% was considered to be acceptable[15] and thus, was targeted in this study; this equated to 130 completed questionnaires.

A review of the literature on the subject guided the development of the questionnaire. To ensure content and face validity the draft questionnaire was reviewed by 2 experts in the fields of ART, pharmacology and anaesthesia. With no corrections required, the final questionnaire was deemed suitable to proceed with data capturing. The questionnaire consisted of two sections and the knowledge section was scored out of 16.

Section 1 sought to obtain the following demographic data: professional designation and years of anaesthetic experience. Section 2 consisted of 13 questions which addressed the anaesthetists' knowledge of ART. The questions were structured as short-answer questions and multiple-choice questions. The questions assessed anaesthetists' knowledge on ART physiological side effects, ART pharmacological interactions with anaesthetic agents, and ART treatment interruption.

Data were collected at the departmental academic meetings at the hospitals associated with the Wits Department of Anaesthesiology over a period of seven months. One author (MO) was present at all meetings to prevent data contamination. Anaesthetists were invited to participate as they arrived at the meeting, and an information letter was given to those who consented. Each questionnaire was allocated a study number and was returned immediately in a sealed envelope.

The data were captured on spreadsheets using Microsoft Excel™ 2010. The scores were presented as percentages rounded off to one decimal place. Questions that were left blank were considered incorrect. Administration of drugs is a core domain in the practice of anaesthesiology highlighting pharmacology knowledge as essential[16] therefore the author defined adequate knowledge as an overall score of $\geq 80\%$. The statistical program, GraphPad InStat, was used to analyse the data. Descriptive and inferential statistics were used and calculations of a t-test and Fisher's exact test were conducted, with a p value of <0.05 considered statistically significant.

Results

Of the 140 questionnaires ten were not included, as five were not returned and five were returned blank. The remaining 130 questionnaires which represented 60% of the department and equated to a 93% sample realisation. The participants' demographics are shown in Table I. Junior anaesthetists included medical officers and registrars, while senior anaesthetists included career medical officers and consultants.

Table I: Demographics of the participants

Demographic	Participants	
Professional designation	Number	Percentage
• Juniors	92	70.8
• Seniors	38	29.2
Years of experience		
• <1	13	10.0
• 1–5	77	59.2
• 6–10	31	23.8
• >10	9	6.9

The overall knowledge of the anaesthetists regarding ART with specific relevance to anaesthetic agents is presented as an overall percentage mean score (SD) achieved by the 130 participants of 50% (18%). Scores ranged between 6 and 94%. Five (4%) of the participants attained a score above 80%. The scores obtained by the participants are illustrated in Figure 1.

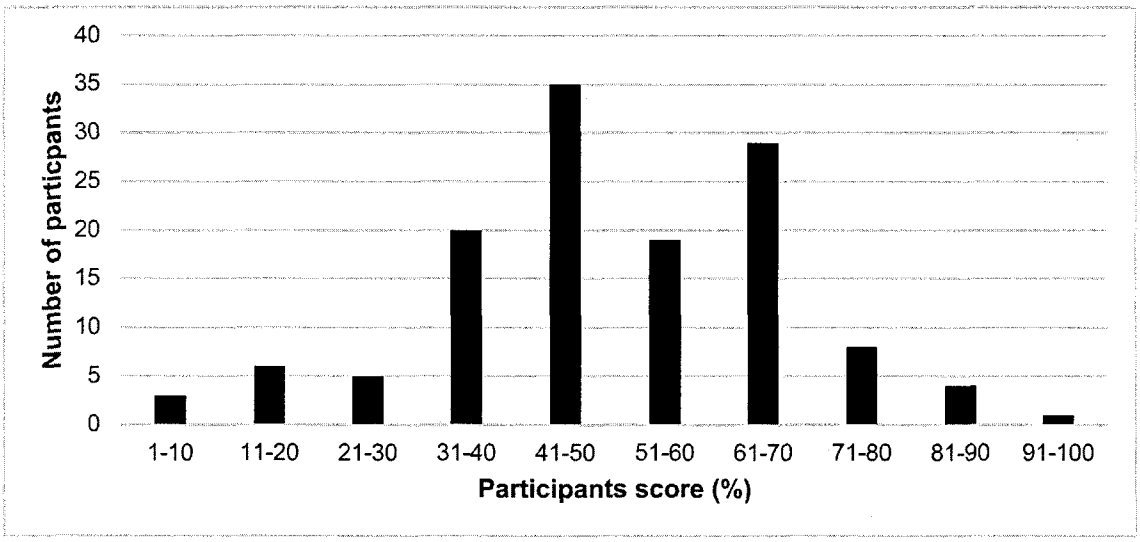

Figure 1 Participants' overall knowledge scores

Table II summarises the results of all the questions included in the questionnaire. The questions were categorised into three subscales according to the knowledge assessed: physiology, pharmacology and treatment interruption. Ten of the questions had one correct answer, while 3 of the questions had 2 correct answers. The results are presented as the number of correct answers and the overall average score for the subscale category.

Table II Subscale knowledge assessed in questionnaire and results

Subscale knowledge assessed	Question description	Correct, n (%)	Subscale average, n (%)
Physiology	Class associated with peripheral neuropathy	64 (49.2)	
Physiology	Pancytopenia associated with AZT	71 (54.6)	
Physiology	Classes of ART that cause lipodystrophy*	87 (66.9)	
Physiology	Classes of ART that cause hepatotoxicity*	68 (52.3)	
Physiology	Cardiovascular effects of ART	9 (6.9)	
Physiology	Causative agents of life threatening complications	89 (68.5)	
			64.6 (49.7)
Pharmacology	Renal dysfunction associated with tenofovir	69 (53.1)	
Pharmacology	Agents susceptible to interactions	52 (40.0)	
Pharmacology	Agents minimally affected	74 (56.9)	
Pharmacology	Nightmares, hallucinations and agitations associated with efavirenz	83 (63.8)	
Pharmacology	Classes that cause lactic acidosis*	72 (55.4)	
			70 (53.8)
Treatment interruption	Consequences of treatment interruption	58 (44.6)	
Treatment interruption	Understanding of preoperative use of ART	107 (82.3)	
			82.5 (63.5)

*Questions that had two correct answers, average score of the two questions was used in calculations in Table II.

When comparing the level of knowledge with professional designation, the mean (SD) score for the juniors, 6.43 (2.3), did not differ significantly ($p = 0.1993$) from the mean (SD) score for the seniors of 7.03 (2.5). Further analysis was done to assess whether more juniors or seniors had passed or failed at the 80% pass mark. For the 80% pass mark, more juniors failed compared to seniors. Among the juniors, one (20%) passed, while among the seniors, four (80%) passed.

Discussion

Anaesthetists are perioperative physicians who administer a variety of drugs in their daily practice, therefore knowledge on pharmacology is a core prerequisite.[9] The literature shows that anaesthetists lack adequate knowledge on the basic pharmacology of many agents relevant to anaesthesia such as local anaesthetic toxicity[17], anaphylaxis[18], cardiopulmonary resuscitation.[19] This is also consistent with a study demonstrating that anaesthetists lack knowledge on a topic central to anaesthetic practice such as pain medications and management, where anaesthetists' average pain pharmacology knowledge score was 61%, with only 22% of the anaesthetists answering all the questions correctly.[24] No literature on anaesthetists' knowledge of ART with specific relevance to anaesthetic agents could be identified.

Since the discovery of HIV as the causative organism of AIDS, it is estimated that 78 million people have become infected with the virus and at least 35 million have died from AIDS.[4] Advances in modern medicine's understanding of HIV, as well as the development of ART, have changed the course of the disease by reducing new infection rates and mortality rates by 49% and 29% respectively.[3] In South Africa, with the population on ART, the disease continues to grow. In 2016 the annual rate of new infections was estimated to be 270 000 per annum.[3] In view of this high HIV prevalence, Wits anaesthetists will encounter many patients on ART.

The poor attendance at academic meetings was a limiting factor in achieving the targeted sample size, resulting in data collection targets achieved after seven months. Despite this, data contamination was prevented by one author present at every meeting, who ensured questionnaires were returned immediately sealed in an envelope to minimise bias. In this study four aspects of ART knowledge were assessed namely: overall ART knowledge score, knowledge of ART side effect profile, knowledge of treatment interruption and experience.

Anaesthetists showed a lack of knowledge, with an overall score of 50%. This is consistent with a study by Arshad et al,[20] in 2009 in Baltimore amongst resident physicians, which found the average ART knowledge score was 35%. In contrast, Rasson et al,[21] in 2007, in Cameroon found a mean knowledge score of 81.4%

amongst doctors, however the better knowledge was attributed to supervised training and experience with ART.

Anaesthetists showed inadequate knowledge of ART systemic side effects scoring a mean of 49,7%. This lack of knowledge is concerning as life threatening complications may go unnoticed in the perioperative period. This is consistent with literature similarly demonstrating inadequate knowledge amongst anaesthetists with regards to physiological effects seen in anaesthesia after laryngoscopy, intubation and neuraxial blockade.[22] Anaesthesia alters a patient's physiology and therefore anaesthetists are responsible and accountable for the care of the unconscious anaesthetised patient.[23]

This study demonstrated anaesthetists' inadequate knowledge with a mean score of 63,5% on the consequences of treatment interruption. Anaesthetists need to be aware of their role in ART treatment interruptions, as treatment adherence is the most significant determinant of ART success.[6] Minimal compliance of 95% is required to prevent treatment failure and the development of resistance.[6] A comparison in the literature was seen in the interruption of antibiotic therapy by internal medicine registrars based in Michigan which is one of the factors that resulted in resistance.[24]

The findings in this study demonstrate no statistically significant difference between professional designations in the department and level of knowledge. Amongst the anaesthetists four seniors passed in comparison to one junior, which is similar to a study of paediatric doctors who demonstrated more drug dosage errors in their junior years of training.[25] It is also consistent with a study by Droste et al[18] which found doctors lack knowledge of adrenaline irrespective of level of seniority or experience where a mean knowledge score on the use of adrenaline was 14%.

When reflecting on the SASA-defined scope of practice for anaesthetists, it is clear that an essential component of the anaesthetists' daily practice is comprehensive knowledge of all medication that a patient may be taking.[16] Inadequate knowledge and experience have been linked to adverse medication related events which can be lethal.[23] Estimates suggest more people die from medication related adverse events than motor vehicle accidents.[23] This study's findings demonstrate lack of adequate knowledge regarding ART

among anaesthetists in a society where the disease is so common. It is possible that this is attributed to ineffective traditional teaching methods, which could be improved by exploring strategies in other institutions that have proved more successful.

Conclusion

The last few decades have seen tremendous growth in the understanding of HIV and ART, resulting in longer life spans for HIV-infected patients. This has resulted in the increased likelihood of these patients requiring surgical interventions and anaesthesia.[10] Hence, anaesthetists' knowledge of ART and its implications is essential.[13] While there is a lack of research on this subject globally, this study does suggest a lack of adequate knowledge on the part of anaesthetists in this institution. Recommendations are made for anaesthesia training programmes aimed at improving knowledge on the subject, in support of the World Health Organisation's sentiments "to ensure the right patient receives the right medication at the right dose via the right route at the right time".[5]

Conflict of interest

The authors declare no financial or personal relationship(s) which may have influenced the writing of this paper.

Acknowledgements

This research was done in partial fulfilment of a Master of Medicine degree. The authors thank Dr Evan Shoul.

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4. Section IV: Appendices

4.1 Ethics approval

R14/49 Dr Maryam Omar

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150712

NAME: (Principal Investigator)	Dr Maryam Omar
DEPARTMENT:	Anaesthesiology University of the Witwatersrand
PROJECT TITLE:	Anaesthetists' Knowledge of Antiretroviral Drugs with Specific Relevance to Anaesthesia
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Helen Perrie
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/12/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

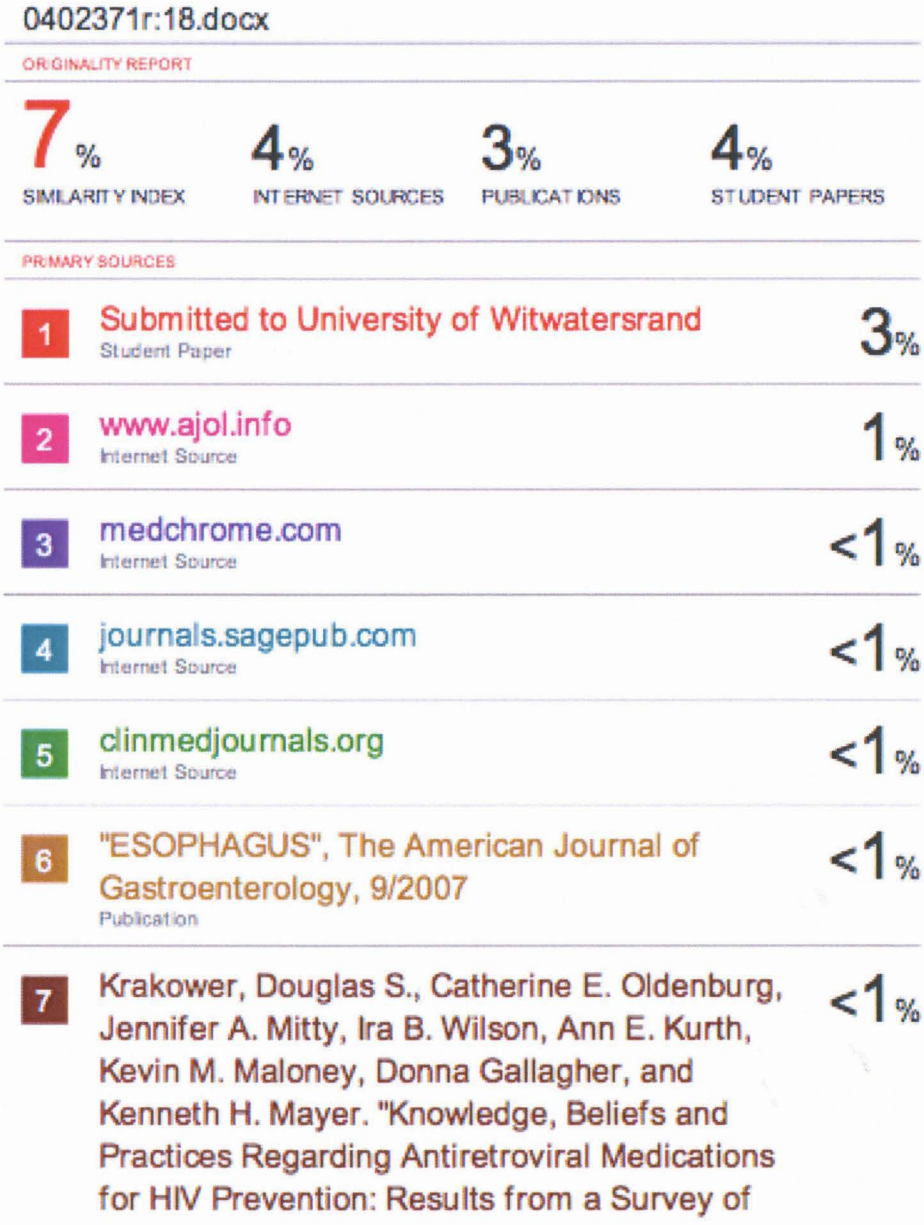
To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

4.2 Graduate Studies Committee approval

4.3 Turnitin report



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5. Section V: Proposal

Anaesthetists' knowledge of antiretroviral drugs with specific relevance to anaesthesia

Maryam Omar

0402371R

Supervisor: Helen Perrie

Department of Anaesthesiology

Co-supervisor: Professor Juan Scribante

Department of Anaesthesiology

Co-supervisor: Professor Analee Milner

Department of Anaesthesiology

5.1 Introduction

As echoed by the sentiments of Nelson Mandela: "HIV/AIDS is the greatest danger we have faced for many, many centuries. HIV/AIDS is worse than a war. It is like a world war. Millions of people are dying from it" (1).

In its fourth decade as a worldwide pandemic, HIV/AIDS universally burdens the health and economic sectors across all continents (2). Africa has been identified as an area of exponential growth and spread. At its most southern tip, South Africa (SA) was estimated to have 6.3 million people living with HIV/AIDS in 2013 (2). According to the World Health Organisation (WHO), the actual worldwide population on antiretroviral treatment (ART) as of 2013 was in the range of 11 to 12 million people (2-4). Projected data for 2015 suggests that worldwide, 15 to 16 million people would be on ART (4). With the advent of ART over the past two decades, life expectancy has increased in HIV positive patients (5). Due to the exponentially growing prevalence of HIV and and patient longevity, healthcare professionals will commonly encounter patients on ART.

Anaesthetists act as the advocate for the patient, while they are under anaesthesia. The patients' comorbid diseases and medication influence the anaesthetists' perioperative plan (6, 7). Estimates show that 20-25% of HIV positive patients require surgery in their lifetime, hence anaesthetists' knowledge regarding ART is essential (5, 6, 8, 9).

ART includes combination regimens of at least three drugs from the different classes of antiretroviral drugs (ARVs), with the main aim to suppress the viral replication whilst retarding the disease progression in order to ultimately improve quality of life (6, 7, 9). ART entails specific combinations of drugs: either one or two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) and/or one protease inhibitor (PI). These categories of NRTIs, NNRTIs and PIs are classed according to common pharmacokinetic and pharmacodynamic profiles. This knowledge is imperative for anaesthetists as each of these classes interacts uniquely with specific anaesthetic drugs, for example NNRTIs and opioids, PIs and benzodiazepines, and NRTIs and

antibiotics (5-7). These interactions are complex and affect dosing and toxicity of a large spectrum of anaesthetic drugs and consequently the perioperative outcomes (7).

In addition to other adverse effects, ART causes chronic lifelong complications as well as acute life threatening effects (2, 9). The commonly known life threatening complications associated with ART are lactic acidosis, immune reconstitution inflammatory syndrome, hepatotoxicity and nephrotoxicity; all of which impact significantly on the anaesthetist's perioperative plan. Chronic complications commonly associated with ARVs manifest in all body systems (5, 8). Thus, the anaesthetist needs to be aware of these acute and chronic complications for appropriate and holistic anaesthetic technique and perioperative management (2, 7).

Due to the perioperative starvation guidelines, it is often found that patients omit their routine medications, including ARVs (7). Clinical trials have shown that interruptions to continuous ART can worsen long-term morbidity and mortality amongst these individuals (10). Interruptions of continuous ART results in the rapid development of drug resistance, development of opportunistic infections and malignancies with subsequent negative impacts on morbidity and mortality (7). The anaesthetist's awareness of and role in the impact of treatment interruption is imperative to the long term outcome of the patient (7).

On reviewing the literature, anaesthetists' knowledge regarding ART has not been described. The literature has rather described the knowledge of doctors, nurses and patients regarding ART. Doctors, nurses and patients all displayed different levels of average knowledge regarding ART, where the level of knowledge displayed was suggested to be proportional to the health professionals level of experience and training in the management and clinical implications of ART (11-13).

5.2 Problem statement

According to WHO, sub Saharan Africa currently has the highest prevalence of HIV positive patients and the largest ART programme (3, 4). In developed countries it is estimated that 20 to 25% of HIV positive patients undergo surgery and are thus exposed to anaesthesia. Despite the increasing prevalence of HIV in SA, the current knowledge of SA doctors on ART is not known. In providing anaesthesia to patients on ART, the drug side effects, drug interactions and perioperative interruption are all important areas of knowledge and expertise for the anaesthetist (6-8). The literature is lacking in the sphere of assessing anaesthetists' knowledge regarding these aspects.

5.3 Aim

The aim of this study is to describe the knowledge of anaesthetists in the Department of Anaesthesiology regarding ART, with specific relevance to anaesthesia.

5.4 Objectives

The primary objectives of this study are to describe the knowledge of the anaesthetists with regard to:

- selected ART interactions with anaesthetic agents
- side effects of ART and their implications for anaesthesia
- perioperative treatment interruption of ART.

The secondary objectives of this study is to compare the level of knowledge with professional designation.

5.5 Research assumptions

The following definitions will be used in the study.

Anaesthetist: is any qualified doctor working in the Department of Anaesthesiology including medical officers, registrars and consultants.

Medical officer: is a qualified doctor practising in the Department of Anaesthesiology under specialist supervision. Medical officers with more than 10 years of experience are career medical officers and are regarded as consultants.

Registrar: is a qualified doctor that is registered with the Health Professional Council of South Africa as a trainee anaesthetist.

Consultant: is a specialist anaesthetist or career medical officer.

Adequate knowledge: in this study adequate knowledge is regarded as a score of 80% or above.

Juniors: includes medical officers and registrars.

Seniors: includes specialist anaesthetist consultants and career medical officers.

5.6 Demarcation of study field

The study will be conducted in the Department of Anaesthesiology, affiliated to the Faculty of Health Sciences of the University of the Witwatersrand (Wits). The staff complement of the department is 85 consultants, 112 registrars and 21 medical officers. The department is affiliated to the following hospitals: Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital, Helen Joseph Hospital, Rahima Moosa Mother and Child Hospital, and Wits Donald Gordon Medical Centre.

5.7 Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand.

The researcher will approach anaesthetists at academic departmental meetings explaining the study and inviting them to participate. If they agree the researcher will give the participants an information letter (Appendix 1) and the questionnaire (Appendix 2). The return of their completed questionnaire will imply their consent.

Anonymity will be ensured by collecting data without individual identifying information, rather a study number will be used for each questionnaire. Confidentiality will be ensured by limiting access to the raw data solely to the researcher and supervisors.

If the outcome of the study shows poor knowledge, the researcher will organise a lecture focusing on ART in anaesthesia. Data will be stored securely for six years after completion of the study. The study will be conducted according to the principles of the Declaration of Helsinki (14) and the South African Guidelines for Good Clinical Practice (15).

5.8 Research methodology

5.8.1 Research design

A prospective, contextual, descriptive research design will be followed in this study. A prospective study selects a group of subjects and observes them over time in the context of the research subject, for specific outcomes (16). This study is prospective as it entails providing questionnaires to anaesthetists at the time of data collection.

According to Strydom et al (17) a contextual study refers to a specific chosen group or population, defined by a "small-scale world" which could be a specific medical discipline ward, an intensive care unit or a clinic. This study is contextual because it is conducted specifically in the Department of Anaesthesiology at Wits.

A descriptive study is where information is collected without experimentally changing circumstances. In research such as this study, a descriptive study can provide information about a chosen aspect of the sample population. In this instance it is describing knowledge amongst anaesthetists. In descriptive studies, the researcher interacts with the sample population via the means of a chosen

instrument to obtain the information of interest (16). In this study, the researcher is interacting with anaesthetists using a questionnaire as the instrument, to obtain the anaesthetists' knowledge regarding ART.

5.8.2 Study population

The study population consists of all anaesthetists working in the Department of Anaesthesiology.

5.9 Study sample

5.9.1 Sampling method

In this study a convenience sampling method will be used. According to Botma et al (18), convenience sampling is a method of non-probability sampling, whereby the researcher includes any participants who happen to be "in the right place at the right time."

5.9.2 Sample size

The sample size will be realised by the number of responses. A response rate of 60% is considered as acceptable.

5.9.3 Inclusion and exclusion criteria

The inclusion criteria for this study are:

- anaesthetists working in the Department of Anaesthesiology
- who were willing to participate in the study.

Blank questionnaires were excluded.

5.10 Collection of data

5.10.1 Questionnaire

No questionnaires pertaining to the knowledge of ARVs specifically amongst anaesthetists has been found in the literature. A draft questionnaire based on a review of the literature was developed to ensure content and face validity. The questionnaire was given to three experts with an interest in ARVs for review, two of whom were anaesthetists and one a physician, to ensure face validity. The experts' suggestions were incorporated in the final questionnaire.

The self-administered questionnaire (Appendix 2) consists of two sections. Section 1 includes the following demographic data: professional designation and years of anaesthetic experience. Section 2 consists of 13 questions addressing the knowledge of anaesthetists regarding ART. The questions are structured as short answer questions and multiple choice questions, and will assess knowledge of anaesthetists regarding specific aspects of ART: the drug interactions with anaesthetic agents, the side effects of ART relevant to anaesthesia and the perioperative treatment interruption.

5.10.2 Data collection process

Each questionnaire will be numbered to keep account of the completed questionnaires. Questionnaires will be distributed at departmental academic meetings. The researcher will approach the convenor for permission to address the meeting. A brief introduction to the study will be provided, followed by an invitation to participate. Those who agree to participate will be provided with an information letter (Appendix 3) along with the questionnaire (Appendix 2). Twenty minutes will be allowed for completion of the questionnaire. The researcher will be present to answer any questions and to prevent data contamination. Completed questionnaires will be placed in a sealed box by the participants.

5.11 Data analysis

Using Microsoft Excel™ 2010, data will be captured onto spreadsheets. The statistical program, GraphPad InStat, will be used to analyse data. Categorical variables will be described using frequencies and percentages. Continuous variables will be described using means and standard deviations or medians and

interquartile ranges, depending on the distribution of the data. Comparison between categorical variables will be done using either Chi squared or Fisher's exact test. A p-value of <0.05 will be considered statistically significant. Any unanswered questions will be considered incorrect.

5.12 Significance of the study

In developed countries it is estimated that 20 to 25% of HIV positive patients will undergo surgery and anaesthesia (5, 6, 8, 19), while in SA there are no recent statistics to quantify this measure. Specifically focusing on ARVs, there is vast knowledge and insight pertinent to the anaesthetist to ensure holistic and thorough perioperative anaesthetic care is delivered to patients taking these drugs. There is limited data and information available indicating the extent of existing knowledge amongst anaesthetists regarding ART (4, 7). Thus, the proposed study will highlight the current state of knowledge of anaesthetists in the Department of Anaesthesiology regarding ARVs, and this may lead to the improvement in the future of anaesthesia for HIV positive patients on ARVs in the Department of Anaesthesiology.

5.13 Validity and reliability of the study

According to Botma et al (18) "validity indicates whether the conclusions of the study are justified based on the design and interpretation." Validity is further explained by the authors as "the degree to which a measurement represents a true value. Validity is always a matter of degree not an absolute."

"Reliability represents the consistency of the measure achieved. Reliability is an indication of the extent of random error in the measurement method." (18) This implies reproducibility of results when applying the questionnaire to different populations.

Validity and reliability of this study will be ensured by:

- using an appropriate study design
- using a questionnaire with face and content validity
- the researcher being the only data collector and being present at the time of data collection to prevent data contamination
- for accuracy of captured data, every tenth entry point on the spreadsheet will be checked
- data analysis done in consultation with a biostatistician.

5.14 Potential limitations of the study

Due to the method of convenience sampling there is a risk of sampling bias. According to Botma et al (18), this is due to the fact that the available participants may not be a typical and true reflection of the population studied and therefore there is no control over the representativeness of the sample. The results of this study may therefore not be generalisible.

This study will be done contextually in the Department of Anaesthesiology at Wits and this may also influence the generalisibility of the results to other contexts.

5.15 Project timeframe

Activity	May 2015	June 2015	Aug 2015	Oct 2015	Nov 2015	Dec 2015	Jan 2016	Feb 2016
Proposal preparation								
Literature review								
Proposal submission								
Ethics and postgrad approval								
Data collection								
Data analysis								
Write article								
Submission								

5.16 Financial plan

The Department of Anaesthesiology will bear the cost of the paper and printing:

Item	**Number**	**Cost**	**Total**
Printing	1000	R1/page	R1000
Binding	4	R50 each	R200
			R1 200

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APPENDIX 1: Information sheet

Dear Colleague,

Hello, my name is Maryam, and I am a registrar in the Department of Anaesthesiology at Wits. I would like to invite you to participate in a research study titled, "Anaesthetists' knowledge of antiretrovirals with relevance to anaesthesia." This study will be in partial fulfilment of my MMed degree.

This study aims to determine the current knowledge of anaesthetists in the Wits Department of Anaesthesiology regarding ARV's side effects, interactions and treatment interruption relevant to anaesthesia.

Participation is voluntary and consent will be implied on completion of a questionnaire. No personal information will be required when completing the questionnaire, therefore anonymity will be maintained. Confidentiality will be ensured as, only the researcher and supervisors will have access to the raw data. No incentives will be provided for participation and there will be no consequences for those choosing not to participate or withdrawing from the study.

Each questionnaire will have a number for the purpose of data capturing. The specific number will not identify the participant involved. The questionnaire should not take longer than 20 minutes to complete and participants are encouraged not to share the information. On completion of the questionnaire, participants are requested to place questionnaires into the sealed box provided.

This study has received ethics (number) and postgrad permission. Before completion of this questionnaire, please ensure that you understand the above information. Any questions regarding this study can be directed to me, Maryam Omar on 083 270 3797, or the Chairperson of the Ethics Committee on (011) 717 1234.

Your time and co-operation are sincerely appreciated.

Yours Sincerely,

Maryam Omar.

APPENDIX 2: Questionnaire

[Total score 16]

SECTION 1: Demographics

Please provide the following information by use of the tick box:

1.1 Professional designation:

Medical Officer	
Registrar	
Career Medical Officer	
Consultant	

1.2 Years of experience in anaesthesia:

<1	
1-5	
6-10	
11-15	
16-20	
>20	

SECTION 2: Anaesthetists' knowledge regarding ARVs

2.1 ARV Interactions with anaesthetic agents: select one correct answer

a) Which anaesthetic agents are commonly susceptible to interactions with ARVs? [1]

Alfentanil, Fentanyl, Midazolam	
Morphine, Lorazepam	
Sufentanil, Tramadol	
All of the above	

b) Which anaesthetic agents are preferred due to minimal interactions with ARVs? [1]

Desflurane, Atracurium, Remifentanil	
Succinylcholine, Gantacurium	
Etomidate, Propofol	
All of the above	

2.2) Drug Side Effects

Which class of ARVs will cause peripheral neuropathy? [1]

Answer: NRTIs

Which ARV can account for conjunctival pallor and pancytopenia [1]

Answer: Zidovudine

Which class of ARVs can result in lipodystrophy? [2]

Answer: NNRTIs/PIs

Which ARVs can affect the cardiovascular system? [1]

Answer: NNRTIs

Which ARVs can cause hepatotoxicity? [2]

Answer: NRTIs/NNRTIs

Which ARV can cause renal dysfunction? [1]

Answer: NRTI – Tenofovir

Which ARVs cause neuropsychiatric symptoms such as nightmares, hallucinations, and agitation? [1]

Answer: Efavirenz

Which class of ARVs can cause lactic acidosis? [2]

Answer: NRTIs and NNRTIs

2.3) Acute life threatening complications: Select one correct answer

In anaesthesia, which of the following are acute life threatening complications associated with ARVs? [1]

lactic Acidosis	
immune reconstitution inflammatory syndrome	
hepatotoxicity and nephrotoxicity	
All of the above	

2.4 Treatment Interruption

a) What are the consequences of perioperative treatment interruption of ARVs? [1]

drug resistance	
increased risk of developing opportunistic infections	
increased risk of malignancies	
all of the above	

b) What should the anaesthetist advise the patient preoperatively regarding their ARV use? [1]

encourage them to omit the dose the night before	
encourage them to omit their medication 7 days prior to the scheduled anaesthetic	
encourage them to take their prescribed ARVs pre-op with water	
none of the above	

Thank you for completing this questionnaire.