A retrospective analysis of potential drug interactions of antiretroviral prescriptions in a section of the private health care sector of South Africa

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Thesis submitted for the degree Doctor of Philosophy in Pharmacy Practice at the Potchefstroom Campus of the North-West University

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November 2009

Dedication

"I dedicate this thesis to all my late relatives, especially my beloved grandmother, and to my dearest father whose wish was for me to become a doctor, to my lovely mother who is always praying and wishing me good luck in every endeavour, to my brothers and sisters for their constant prayers. To my darling husband who is always there for me, to my lovely three sons for their encouragement and psychological support."

ACKNOWLEDGEMENTS

It is not possible to acknowledge all the people, institutions and organisations who in one way or another made a great contribution to the successful completion of this study. However, I would like to thank the following:

- **My promoters: Prof M.S. Lubbe** for the constant guidance right from the start to the end of this study. Thank you for demonstrating to me the high standards of professionalism in Pharmacy Practice.
- **Prof. J.H.P. Serfontein** and **Prof. I. Truter** for their supervision and direction throughout this long journey.
- **Dr. J. Bodenstein** for his professional advice with chapter 2 and article no 6.
- **The Head of Pharmacology Department and Staff, Walter Sisulu University: Prof. E. N. Kwizera,** for allowing me to expand my academic endeavours. **Prof. O. Meissner** for her constant professional advice and motherly care. **Prof. Y. Dambisya,** former colleague, for his constant encouragement and advice. **Prof. J. Aguirre** for the academic support.
- **The Managers of the two South African PBM companies** for granting permission to get access to the data utilised in this study project.
- **To MRC** for the financial assistance towards the research project.
- **Ms. M. Terblanche** for friendly support and accurate English language editing of the thesis.
- **Prof. J. Breytenbach** for the language editing of the Afrikaans summary.
- **The North-West University (Potchefstroom Campus)** for admitting me to the Doctorate programme and **Pharmacy Practice staff** for their warm welcomes during my visits to the university.
- **My Family**: My husband, **Lucky** who gave me full support, encouragement and all the love as I went through this difficult journey. My three sons: **John Francis, Simon Peter and Jimmy James** who were always there for me to offer any assistance.
- My mother, sisters, brothers and relatives in Uganda, I say thanks to you all.
- The Lord God Almighty: For the gift of life coupled with strength, good health, courage to start and complete this study programme.
- To all my friends who in one way or another made a great contribution towards the completion of this PhD.

Norah Lucky Katende-Kyenda

9 November 2009

PREFACE

For the purpose of this study, the article format is used and, therefore, Chapter 3, the chapter containing results, is in the form of articles as required by the regulations of the North-West University. Five manuscripts were submitted and published in the following journals and one manuscript is still under review:

- *South African medical journal.*
- *Journal of clinical pharmacy and therapeutics.*
- *International journal of pharmacy practice.*
- *African journal of primary health care and family medicine,*
- *International journal of STD & AIDS,*
- *Journal of pharmacoepidemiology and drug safety* (Manuscript under review)

For the individual articles all the references are cited according to the instructions for authors as issued by the different journals. However, a bibliography is at the end of the thesis according to the reference style of the North-West University.

Chapter 1 is an introductory chapter with the background to the study. It contains a literature review on Health Care in South Africa. Chapter 2 is an extensive literature review regarding the recommended management guidelines and drug-drug interactions for HIV/AIDS. In Chapter 4 the discussion of the general findings to the study is given, conclusions, recommendations and specific limitations of the study are described. The promoter and co-promoters are named in the articles as co-authors and during the study they acted in the specific roles of promoter and co-promoters. They also gave consent that the articles could be used as part of this thesis. The specific contribution of each author during the study is given on the next page.

AUTHORS' CONTRIBUTIONS

The contribution of each author in the study is set out in the following table.

Author	Role in the study
Mrs. N. L. Katende-Kyenda	Responsible for the literature search. Planning and design of study and manuscripts. Statistical analysis. Interpretation of results. Report writing.
Prof. M.S. Lubbe (Promoter)	Supervision of original planning and design of study and manuscripts. Statistical analysis. Guidance in the interpretation of results. Supervised the writing of the manuscripts and thesis.
Prof. J.H.P. Serfontein (Co-promoter)	Involvement in planning and design of study and manuscripts. Guidance in the interpretation of results. Supervised the writing of the manuscripts and thesis.
Prof. I. Truter (Co-promoter)	Involvement in planning and design of study and manuscripts. Guidance in the interpretation of results. Supervised the writing of the manuscripts and thesis

The following is a statement provided by the co-authors to confirm their individual roles in the study and give their permission that the articles may form part of this thesis.

I declare that I have approved the above-mentioned articles, that my role in this study, as indicated above, is representative of my actual contribution and that I hereby give my consent that it may be published as part of the PhD thesis of Norah L. Katende-Kyenda.

Prof. M.S. Lubbe

Prof. J.H.P. Serfontein

Prof. I. Truter

ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ADI	Adverse drug interaction
ADR	Adverse drug reaction
AfA	Aid for AIDS
ALT	Alanine transaminase
APV	Amprenavir
ART	Antiretroviral therapy/treatment
ARV(s)	Antiretroviral(s)
AUC	Area under the curve
AZT	Azidothymidine
BID	Twice daily
CCEB/DBE	Centre for Clinical Epidemiology & Biostatics/Department of Biostatics and Epidemiology
CD4	Cluster of differentiation
CDL	Chronic disease list
COHSASA	Council for Health Service Accreditation of Southern Africa
COPD	Chronic obstructive pulmonary disease
CPK	Creatinine phosphokinase
CVD	Cardiovascular disease
CYP450	Cytochrome P 450
D4T	Stavudine
ddc	Zalcitabine
DDI(s)	Drug-drug interaction(s)
ddl	Didanosine
DHHS	Department of Health and Human Services
DSP	Designated Service Provider
DRV	Darunavir
DUR	Drug utilisation review
EM	Emergency department
EFV	Efavirenz
FDC	Fixed dose combination

FPV	Fosamprenavir
FTC	Emtricitabine
GEMS	Government employees medical scheme
GP(s)	General practitioner(s)
HAART	Highly active antiretroviral therapy
HAQU	Health care accreditation and quality unit
HASA	Hospital Association of South Africa
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV/AIDS	Human immunodeficiency virus/acquired immune deficiency syndrome
HPCSA	Health Professions Council of South Africa
HSRC	Human Sciences Research Council
ICD	International Classification of Diseases
IDU	Injecting drug use
IND	Indinavir
ICP	Infection control programme
ISO	International Organisation for Standardisation
ISQua	International Society for Quality in health care
IV	Intravenous
LPP	Limited private practice
LPV/RTV	Lopinavir/ritonavir
MIMS	Monthly Index of Medical Specialities
MRC	Medical Research Council
MTCT	Mother-to-child-transmission
MVC	Maraviroc
NADPH	Nicotinamide adenine dinucleotide phosphate
NAPPI	National Pharmaceutical Product Interface
NETCARE	Network Health Care Holdings Limited
NFV	Nelfinavir
NHS	National Health Service
NNRTI(s)	Non-nucleoside reverse transcriptase inhibitor(s)
NRF	National Research Foundation
NRTI(s)	Nucleoside/nucleotide reverse transcriptase inhibitor(s)
NSAID(s)	Nonsteroidal anti-inflammatory drug(s)

NVP	Nevirapine
NWU	North-West University
LFT(s)	Liver function test(s)
OD	Once a day
OIs	Opportunistic infections
PBM	Pharmacy Benefit Management
PCP	Pneumocystis pneumonia
PCR-DNA	Polymerase chain reaction-deoxyribonucleic acid
PDD(s)	Prescribed daily dose(s)
PEP	Post exposure prophylaxis
PHC	Primary health care
PHTF	Public Health Service Task Force
PI(s)	Protease inhibitor(s)
PIASA	Pharmaceutical Industry Association of South Africa
PMBs	Prescribed Minimum Benefits
PO	Oral
PPI(s)	Proton pump inhibitor(s)
QID	Four times a day
RFB	Rifabutin
RMP	Rifampicin
RTV	Ritonavir
SA	South Africa
SABCOHA	South African Business Coalition on HIV/AIDS
SAHRC	South African Human Relations Council
SAMF	South African Medicines Formulary
SAQ	Saquinavir
SARB	South African Reserve Bank
SAS	Statistical analysis system
SP(s)	Specialist(s)
SSRI(s)	Selective serotonin reuptake inhibitor(s)
TB	Tuberculosis
TDF	Tenofovir
UK	United Kingdom
UNAIDS	United Nations programme for HIV/AIDS
UNICEF	United Nations Children's Fund

OPSOMMING

'n Retrospektiewe ontleding van moontlike geneesmiddelinteraksies op antiretrovirale voorskrifte in 'n deel van die private gesondheidsorgsektor in Suid-Afrika

Sleutelwoorde:

Antiretrovirale middels, geneesmiddelinteraksies, menslike immuniteitsgebrekvirus (MIV), verworwe immuniteitsgebreksindroom (VIGS), private gesondheidsorgsektor, voorgeskrewe daaglikse dosisse, apteekvoordelebestuursorganisasie

Geneesmiddelinteraksies (GMI's) is 'n ernstige komplikasie as gevolg van die gelyktydige gebruik van meer as een geneesmiddel en is 'n belangrike bron van mediese foute wat grootliks oor die hoof gesien word. Na wat berig word was GMI's met antiretrovirale middels die oorsaak van 5.2% van pasiënttoelatings in 'n hospitaal in Baltimore. Kliniese-beduidende GMI's is algemeen en het ten minste 14% pasiënte in die Verenigde State van Amerika en 23% tot 26% van MIV-geïnfekteerde pasiënte in Nederland aangetas. Antiretrovirale middels wat vir die behandeling van menslike immuniteitsgebrekvirus (MIV)-infeksie gebruik word, is geneig tot GMI's omdat hulle deur die sitochroom P (CYP) 450-stelsel gemetaboliseer word. Verder lei toksisiteit en komplekse dosering tot nie-meewerkendheid van pasiënte met gevolglike mislukking van behandeling en ontwikkeling van weerstandige stamme wat die behandeling van hierdie chroniese siekte kompliseer. Die algemene doel van hierdie studie was om die *voorkoms van moontlike GMI's tussen antiretrovirale middels te ondersoek in 'n deel van die private gesondheidsorgsektor deur medisyne-eise data van apteekvoordelebestuursorganisasies in Suid-Afrika te gebruik.*

Die studie was 'n nie-eksperimentele, kwantitatiewe, retrospektiewe ontleding van antiretrovirale middels op voorskrifte wat deur twee nasionale databasisse, A en B, van twee Suid-Afrikaanse apteekvoordelebestuursorganisasies geëis is. Databasis A het data van 2004 tot 2006, en databasis B het data van 2005 tot 2007, bevat. Die fokus was op die voorkoms van moontlike GMI's tussen antiretrovirale middels wat by die Medisynebeheerraad in Suid-Afrika geregistreer is. Data is met die Statistical Analysis System®, SAS 9.1® ontleed. Moonlike GMI's is volgens Tatro (2008) se kliniese riglyne geïdentifiseer. Die resultate van die empiriese studie is in ses navorsingsartikels gerapporteer en bespreek.

- In albei databasisse was daar 'n toename oor tyd in die aantal MIV/VIGS-pasiënte.
- In albei databasisse was daar meer vroulike as manlike MIV/VIGS-pasiënte wat ook in 2008 deur Statistiek Suid-Afrika bevestig is.
- In databasis A is moontlike GMI's geïdentifiseer tussen antiretrovirale middels (ritonavir, saquinavir en indinavir) en ander middels (lansoprasool, simvastatien, ko-trimoksasool).
- Die meeste antiretrovirale middels interreageer op klinies beduidende vlak 2 (wat 'n pasiënt se kliniese status matig versleg en verdere behandeling vereis) met die hoogste persentasie van moontlike GMI's in databasis A in die ouderdomsgroep 40 tot 60 jaar, en 19 tot 45 jaar in databasis B.

- Gedurende 2005 was daar, vergeleke met 2004, 'n afname in die persentasie GMI's tussen antiretrovirale middels en ander middels (klinies beduidende vlak 1), vanweë die moontlike impak van voorgeskrewe minimum voordele wat op MIV/VIGS gedurende 2005 in Suid-Afrika geïmplementeer is. Daar was in 2005 egter 'n toename in moontlike GMI's op klinies beduidende vlak 2 tussen antiretrovirale middels onderling vergeleke met 2004.
- Verder is moontlike GMI's tussen antiretrovirale middels self geïdentifiseer en meestal tussen die nie-nukleosied omgekeerdetranskriptaseremmers soos efavirens en proteaseremmers soos ritonavir. Van die proteaseremmers het ritonavir die hoogste voorkoms vir moontlike GMI's gehad wat almal op klinies beduidende vlak 2 met saquinavir, indinavir en nevirapien interreageer.
- Die hoogste voorkoms van GMI's, in databasis B, tussen antiretrovirale middels (klinies beduidende vlak 2) in 2005 en 2006 was met kombinasies van drie middels, en in 2007 met twee middels .
- Die resultate toon dat monoterapie steeds in hierdie deel van die private gesondheidsorgsektor voorkom.
- Moontlike GMI's geïdentifiseer tussen antiretrovirale middels met voorgeskrewe daaglikse dosisse wat nie volgens die aanbevole dosering van antiretrovirale middels was nie, was meestal met kombinasies van lopinavir/ritonavir in voorgeskrewe daaglikse dosisse van 799.8 mg/198 mg en efavirens 600 mg, gevolg deur indinavir 1600 mg en ritonavir 200 mg, en dan ritonavir 200 mg en efavirens 600 mg.
- Die voorkoms van voorskrifte vir antiretrovirale middels met moontlike GMI's tussen antiretrovirale middels met voorgeskrewe daaglikse dosisse wat nie volgens die aanbevole dosering van antiretrovirale middels was nie, het van 2005 tot 2007 op voorskrifte deur sowel algemene praktisyns (AP's) as spesialiste (SP's) toegeneem.
- Geïdentifiseerde regimens met GMI's en voorgeskrewe daaglikse dosisse nie volgens die aanbevole dosering van antiretrovirale middels nie, het voorgekom met lopinavir/ritonavir in voorgeskrewe daaglikse dosisse van 1066.4 mg/264 mg en efavirens in voorgeskrewe daaglikse dosisse van 600 mg wat in al drie jare hoër was vir AP's as vir SP's. Hierdie regimens is in die drie jaar die meeste vir pasiënte in die ouderdomsgroep 19 to 45 jaar voorgeskryf.

Die kliniese belangrikheid van die geïdentifiseerde GMI's is volgens die kriteria in die literatuur beoordeel. Geen kliniese beoordeling van die werklike effekte van hierdie interaksies was moontlik nie. Die resultate beklemtoon egter die waarskynlikheid van moontlike GMI's wat in hierdie deel van die private gesondheidsorgsektor van Suid-Afrika tot ernstige probleme kon gelei het. Dit word aanbeveel dat die beheer van hierdie GMI's tussen antiretrovirale middels in kliniese praktyk volgens die aanbevole riglyne vir behandeling gedoen word. Aanbevelings vir verdere studies is geformuleer.

- There was a decrease in the percentage of DDIs between ARVs and other drugs (clinical significance level 1) for 2005 as compared to 2004 due to the possible impact of PMBs on HIV/AIDS implemented in South Africa in 2005. However there was an increase in possible DDIs between ARVs interacting with each other at clinical significance level 2 for year 2005 as compared to year 2004. This was due to implementation of prescribed minimum benefits (PMB) for HIV/AIDS with many medical schemes contracted, registering more HIV/AIDS patients resulting in the increase in the number of ARV prescriptions and therefore DDIs between them.
- Furthermore potential DDIs were identified between ARVs themselves, mostly the non-nucleoside reverse transcriptase inhibitors like efavirenz and protease inhibitors like ritonavir.
- Among the protease inhibitors, ritonavir presented with the highest prevalence of prescriptions with potential DDIs all interacting at clinical significance level 2 with saquinavir, indinavir and nevirapine.
- The highest prevalence of ARV prescriptions with highest potential for DDIs identified, in database B, between ARVs (clinical significance level 2) was in triple-therapy combinations for years 2005 and 2006 and in dual-therapy for year 2007 in database B.
- The results reveal that monotherapy still existed in this section of the private health care sector.
- Potential DDIs identified between ARVs with prescribed daily doses (PDDs) not according to the recommended ARV dosing, were mostly in combinations of lopinavir/ritonavir (protease inhibitors) at PDD of 799.8 mg/198 mg and efavirenz (EFV) 600 mg, followed by indinavir (IND) (protease inhibitors) 1600 mg and ritonavir (RTV) (protease inhibitors) 200 mg, then RTV 200 mg and EFV 600 mg.
- The prevalence of ARV prescription with potential DDIs between ARVs and with prescribed daily doses not according to the recommended ARV dosing increased from 2005 to 2007 for both general practitioners (GPs) and specialists (SPs) prescriptions.
- Identified regimens with DDIs and prescribed daily doses not according to the recommended ARV dosing were between lopinavir/ritonavir at prescribed daily doses 1066.4 mg/264 mg and efavirenz at PDD 600 mg being higher in GP as compared to SP prescriptions. These regimens were mostly prescribed to patients in the age group older than 19 to 45 years for the three years.

The clinical relevance of the identified potential DDIs was evaluated according to criteria stated in the literature. No clinical evaluation of the real effects of these interactions was possible. However, the results emphasised the possibility of the potential DDIs that could have led to severe problems in this section of the private health care sector in South Africa. It is recommended that the management of these potential DDIs between ARVs in clinical practice be done in accordance with the recommended treatment guidelines. Recommendations regarding further studies were formulated.

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CHAPTER 1
INTRODUCTION

In this chapter, the background to the study will be outlined, followed by the aim and objectives as well as the research methodology. The South African health care system plus accessibility and delivery in terms of both public and private health care will be addressed with specific emphasis on the delivery of human immunodeficiency virus/acquired immunodefiency syndrome (HIV/AIDS) treatments within the framework of Prescribed Minimum Benefits (PMBs). Thereafter an overview of the methodologies used to generate results for the individual articles published (or in review) will be provided.

1.1 BACKGROUND TO THE STUDY

Human Immunodeficiency Virus (HIV) represents a major medical problem worldwide, affecting more than 42 million people, with 5.7 million infected in South Africa (UNAIDS/WHO, 2008a:4). The chronic nature of this virus requires the effectiveness of lifelong highly active antiretroviral therapy (HAART), to change the natural history of HIV and continually suppress its replication, thus reducing morbidity and mortality (Yeni *et al.*, 2002:222). Management of HIV/AIDS with HAART is a major challenge faced by health care providers because of treatment barriers such as drug-drug interactions (DDIs), leading to patient non-adherence and development of resistant strains (Fargon & Piliero, 2003:433). DDIs represent a significant opportunity cost to health care systems (Seden *et al.*, 2009:5). The focus of this study, therefore, was to assess retrospectively the prevalence of potential DDIs between antiretroviral drugs (ARVs) in a section of the private health care sector, utilising medicine claims data from pharmacy benefit management (PBM) companies in South Africa.

South Africa (SA), a country at the foot of the African continent, had a population of 48.7 million by mid-year 2008, of which 52% (approximately 25.2 million) were females and 48% males (Statistics South Africa, 2008:5). Of these, 45% live in urban areas, 10% in periurban areas and 45% in neither of the two areas (Statistics South Africa, 2008:3). According to McLeod (2005:137), the South African health care system is composed of a public and a private sector with a grave disparity between the two.

In a draft paper of the United Nations Research Institute for Social Development (URISD) prepared by Wadee *et al.* (2003:4), the South African policymakers had a challenge of redressing the inequity in access to health care services between the public and private sectors. The private sector with about 160 medical

schemes caters for about 8.8 million (18%) of the population, while the public sector caters for the rest of the population (Medical Schemes South Africa, 2009; Da Silva & Wayburne, 2008:39).

After 1994, the model of Primary Health Care (PHC) was mainstreamed in SA, as a people-oriented health care system. After the installation of Mr. Nelson Mandela as the country's president, PHC in the public sector clinics was declared 'free' at the point of delivery to the communities across the nine provinces (Kautzky & Tollman, 2008:18). A national PHC supervision rate of 70% was attained in 2007/2008, with the Department of Health appointing the University of KwaZulu-Natal to develop a National Comprehensive Manual on Infection Prevention Control (IPC) Programme (Department of Health, 2008a:50). A report on health care in SA (Bassett, 2009) indicated that the government annually spends the equivalent of approximately US$3.1 billion (R31 billion) on 39.9 million people, while the private sector spends US$36.5 billion (R365 billion) on just 8.8 million people.

While the private sector is well-equipped with sophisticated technology, it serves only 18% of the population (Chetty, 2009). An analysis of the expenditure on benefits for 2006 annual report indicated that expenditure on private hospitals actually increased by 12.5% to R274 million from R243 million reported in 2005 (Mncebisi, 2007:1). Expenditure on medicines dispensed by pharmacists and providers other than hospitals increased by 8.8% to R8.7 billion from R8.0 billion reported in 2005 (accounting for 17% of schemes benefits in 2006).

The other findings of the final report (Mncebisi, 2007:1) indicated that expenditure on hospital services accounted for R17.9 billion, or 35% of the total benefits paid to providers. Of the R17.9 billion spent, private hospitals' expenditure accounted for R17.7 billion – an increase of 13.6%. Payments to medical specialists accounted for R11 billion, representing a year-on-year increase of 17%. Medical specialists received 21% of benefits paid in 2006 while general practitioners received R4.4 billion, or 8.6% of total benefits paid.

Mcleod and Ramjee (2007:51) stated that the total contributions to medical schemes increased from R11.299 billion in 1994 (R21.869 billion in 2005 Rand terms) to R54.193 billion in 2005. Total contributions were reported to be R57.568 billion in 2006. The average amount contributed per beneficiary per month increased from R343.67 in 1994 (2005 Rand terms) to R660.66 in 2005. This represented nearly a doubling in the average cost contributed per beneficiary per month.

In an annual report of the Council for Medical Schemes for 2007 to 2008 (Willie *et al.*, 2008:2), it was indicated that of the total amount spent on health care by medical schemes, R20.2 billion (36.0%) was to hospitals. There was an increase in expenditure on private hospitals by 12.5% to R19.9 billion in 2007. The

number of beneficiaries admitted to private hospitals (Willie *et al.*, 2008:2) increased to 180 per 1 000 beneficiaries in 2007 compared to 171 per 1 000 in 2006. There are more than 200 private hospitals owned by consortia of private physicians or large corporations.

In the public sector, financial limitations are aggravated by provincial inequities in service delivery especially in poorer provinces. According to the Intergovernmental Fiscal Review (IFR) (Seria, 2003), provincial spending on social services, such as education, health and social welfare have remained stable in recent years, but substantial inequalities still exist amongst provinces. Provinces that have had to incorporate former homeland administrations, such as Limpopo, Eastern Cape and KwaZulu-Natal, typically spend more on high wage bills, leaving less of their budgets for service delivery.

Provincial inequalities also exist in the health sector, hampering service delivery mainly in poorer provinces. Although the provincials health budget was meant to increase from R33.2 billion in 2002-2003 to R36.9 billion in 2003-2004 (Seria, 2003), expenditure per capita varied widely amongst provinces. Limpopo spent R586 on an uninsured person; North-West spent R628, while Gauteng's expenditure per capita was R1580. A report from the PHC financing in the public sector (Blecher *et al.*, 2008:181) revealed that district health services were estimated to grow by 8.2% where most PHC services were located.

Expenditure on staff costs in the health sector has fallen steadily in recent years, from 64.2% of the provincial health budget in 1999-2000 to 58.1% in 2002-2003 (Seria, 2003), but was expected to increase in the next few years as government would try to improve the distribution and retention of health personnel. According to Seria (2003) scarcity of health professionals is a serious problem in mainly rural provinces. For example, one dentist in the Eastern Cape is required to service 190 117 people who use the public health service (Seria, 2003), compared to 25 458 people in Gauteng. In Limpopo, one pharmacist services 48 067 people, compared to 18 994 people in Gauteng. The higher growth in poorer provinces confirmed the trend towards improvement in interprovincial equity and towards equalisation of access to grants and accessibility to medicines like ARVs (Wilson & Blower, 2007:16).

The funding in the public and private sectors is such that private health insurance fees are usually split 50/50 between employers and employees. The public service is funded at national (20%) and provincial (80%) levels (Department of Health, 2002:49). Unfortunately there is a serious discrepancy in health spending between the nine provinces (Bassett, 2009) as reported in Health Care in SA, with some rural areas actually cutting health budgets in favour of education or other social projects, for example housing (Day & Gray, 2007).

Reports from the Ministry of Finance, SA, to the National Council of provinces, estimated that health care services funding could escalate to R200 billion by 2009/2010, equivalent to 8.4% of the Gross Domestic Product (GDP). In the public sector it was projected to have grown from R48 billion to R97 billion (7% annually), while in the private sector, it grew from R78 billion to R129 billion (3.2% annually in real terms) (Republic of South Africa, 2007:3) Aproximately 8.8 million of the population belongs to a private health insurance, and an estimated 30% of those without insurance, occasionally consult doctors on a direct-paying basis, 2% seek primary care services and 28% utilise public hospitals (Havenmann & Van der Berg, 2002:23).

The Human Sciences Research Council (HSRC) in collaboration with Whiteford (2004), a South African economist, generated estimates about poverty in SA. Approximately 57% of individuals in SA were living below the poverty income line in 2001, unchanged from 1996. Limpopo and the Eastern Cape had the highest proportion of poor with 77% and 72% (Whitefold, 2004) of their populations living below the poverty income line, respectively. The Western Cape had the lowest proportion in poverty (32%), followed by Gauteng (42%).

The high levels of poverty (71% in rural areas and 50% overall) and unemployment (at least 23%) make it difficult for people to have any medical insurance to pay for their health needs, placing immense strain on the public sector, and more especially HIV/AIDS greatly reduces annual economic growth, mainly by lowering the long-run rate of technical change (Thurlow *et al.*, 2009:18; Department of Health 2009a). Less than 18% of citizens belong to a medical scheme, with 85% of these people left to consult traditional healers, some of whom are trained by the Department of Health to provide PHC (Medical Schemes South Africa, 2009).

When it comes to the quality of care in each system, the private sector offers excellent services in that the United Nations (UN) ranked South Africa's private health system 39th out of 162 nations (Bassett, 2009) for technological innovation and achievement. Inclusive worldwide people fly to SA for operations that are relatively cheaper, and take advantage of the excellent medical care (MacFarlane, 2008). This may also involve the treatment of HIV/AIDS patients. Despite a massive building programme in the public sector, standards vary from province to province, in that many rural hospitals are run-down, with broken equipment, two patients per bed, and a shortage of basic medicines (Department of Health, 2008a:63). Tshabalala (2005:V) researched on mobile clinic users opinions on the health care service provision in the Muldersdrift area, Gauteng province and reported that lack of well-developed infrastructure and poor roads contribute to inaccessibility of health care services in rural and semi-rural areas. Health programmes are often of poor quality or offer incomplete services. Factors such as lack of knowledge of available health care services, dissatisfaction with the quality and range of services provided, and unavailability of the mobile clinic service when there is a health need, can result in the mobile health care clinic being less utilised.

An annual report of the Council for Medical Schemes for 2007 and 2008 (Willie *et al.*, 2008:3) on medical schemes, stated that of the total amount spent on health care in 2007, the medical schemes paid R9.4 billion (or 16.7%) on medicines dispensed by pharmacists and providers other than hospitals, and this was an increase of 8.8% compared with the R8.7 billion spent in 2006, accounting for 17% of medical schemes benefits in 2006. According to the South African Health Review (Gray & Jack, 2008:44) on medicine pricing regulations, a possibility of renewed litigation was raised by dispensing practitioners, who remained bound to the initial dispensing fee (in their case, 16% capped at a maximum of R16 per item), with annual increases in the single exit price.

The Medical Schemes Act (131/1998) and its subsequent Regulations came into effect in February 1999, as a deregulation to the escalating costs of health care in SA. The Act through the South African Parliament, established a statutory body called the Council for Medical Schemes, to provide regulatory supervision of private health financing through the medical schemes (Council for Medical Schemes, 2009a). Annexure A to the regulations defined the PMBs in terms of 270 diagnosis-treatment pairs. The regulations of November 2002 provided substantial clarifications of the PMB requirements and defined emergency procedures and the need for designated service providers. These PMBs were extended from 1 January 2004, with the introduction of a '*Chronic disease list*' (CDL), which defined 27 chronic conditions considered to be life-threatening, including HIV/AIDS (McLeod, 2005:151).

The PMBs for HIV/AIDS came into effect from January 2000 but only included the treatment and management of opportunistic infections and localised malignancies (McLeod *et al.*, 2003:80; da Silva & Wayburne, 2008:40). Then as from 1 January 2003, PMBs for HIV/AIDS were extended to include a further package of benefits in respect of HIV/AIDS-related conditions that included voluntary counselling and testing (VCT), treatment for tuberculosis (TB), sexually transmitted infections (STIs), mother-to-child transmission (MTCT) of HIV and post-exposure prophylaxis (PEP) following sexual assault (McLeod *et al.*, 2003:81; McLeod, 2005:152). Then following Cabinet's commitment to the provision of antiretroviral therapy (ART) and the publication in 2003 of an "*Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa*", ART was included as part of the PMBs from January 2005 (da Silva & Wayburne, 2008:40).

Drugs can be useful tools in the prevention and treatment of symptoms and a chronic disease like HIV/AIDS requires life-long multi-drug ARV therapy combinations referred to as HAART to completely suppress the HIV-1 replication (Marfatia & Smita, 2005:40). However, HAART is complicated by DDIs, which further complicates management of HIV infection (Clarke *et al.*, 2008: HS-3).

The problem statement will cover aspects of the South African health care system and its challenges. Thereafter the prevalence of HIV/AIDS in SA and other countries will be elucidated. Then a discussion on South African medical schemes will follow, followed by changes in the regulation of the Medical Schemes Act (131/1998), which led to the implementation of PMBs and PMBs for HIV/AIDS will follow. Next the management of HIV/AIDS in the public and private sectors in SA in comparison with other countries will be discussed. Finally a brief introduction of DDIs, as a complication to HIV/AIDS management using HAART will be provided.

1.2 PROBLEM STATEMENT

This section will focus on the South African Health Care Health Care system in terms of the private and public sector and the challenges faced by the two systems.

1.2.1 Health care in South Africa (SA)

The South African health care system is composed of a large public sector and a smaller but fast-growing private sector. Health care varies from most basic PHC, offered free by the state, to highly specialised highly technological health services in the private sector for those who can afford it (Gibson, 2004:2014). The public sector is under-resourced and over-used. According to Ensor (2006), the public hospitals received only 52% of the funds necessary to provide reasonable services, with 10.4% fewer hospitals for the sick than there should have been. According to the South African Health Review (Sanders & Lloyd, 2005:78), it was reported that of those health care professionals registered with their respective professional councils, only 11% of pharmacists, less than 50% of nurses and approximately 25% of doctors, serviced the public health care sector. However, the private sector runs largely on commercial lines, catering to middle- and high-income earners who are members of the medical schemes. According to Da Silva and Wayburne (2008:39) approximately 18% of the SA population was covered by medical schemes while a recent report by Van Eeden (2009:1) stated that 14.3% of the SA population was covered by some form of health insurance.

The state contributes about 40% of all its expenditure on health, thus putting the public sector under pressure to offer services to about 82% of the population, while the private sector covers the health needs of the remaining 18% of the population (Council for Medical Schemes, 2006). Medical schemes cover less than 18% of the population and include high- and middle-income formal sector workers and sometimes their dependents. There are more than 100 medical schemes, and each scheme has a number of benefit packages, so there is considerable fragmentation into many small risk pools.

The remaining 82% of the population is largely dependent on tax-funded health services, and comprises low-income formal sector workers, informal sector workers, the unemployed and the poor. A small part of this population pay out-of-pocket to purchase primary health care services in the private sector, but are entirely dependent on the public sector for hospital services (McIntyre *et al.*, 2008:871). A report from the Health Economics Unit - University of Cape Town, McIntyre and Thiede (2008:36), indicated that in 2005, health care expenditure in SA was slightly more than R100 billion, an equivalent to 7.7% of the GDP in that year.

Private hospitals play a significant role in the South African health care system. A report by the Council for Medical Schemes (Matsebula & Willie, 2008:165) stated that most health professionals, except nurses, work in private hospitals. With the public sector's shift in emphasis from acute to PHC, most private hospitals took over tertiary and specialist health services (Department of Health, 2008a:50). Access to private hospitals is mostly limited to only the beneficiaries of medical schemes, with the changing preference of the medical scheme population to utilise more private hospitals over the public hospitals. As a result, private hospitals experienced substantial growth with the total number of the private sector beds increasing by 32% since 1998 to the current estimate of 27 500 beds (Council for Medical Schemes, 2009a:16).

According to the South African Health Reviews (Boulle *et al.,* 2000), this occurred at a time when the public sector reduced the number of beds in virtually every province. A report from the South African National Health accounts (Cornell *et al.,* 2001:163) stated that in 2001 Gauteng, Western Cape and KwaZulu-Natal had the highest concentration of private hospital beds per 1000 medical scheme population with 95, 39 and 27 beds per 1000 medical scheme population respectively, while Limpopo, Eastern Cape and Mpumalanga had the lowest numbers of hospital beds per 1000 medical scheme population with 5, 13 and 9 beds respectively.

According to the Council for Medical Schemes (Matsebula & Willie, 2006:164) in 2006, there were nine categories of stakeholders in the private hospital industry, with Netcare, Medi-Clinic and Life Healthcare being the largest hospital groups collectively accounting for 66.5% of all private hospitals, 75.6% of all private hospital beds and 80% of ownership of theatre. Of the three, Netcare owned the highest number of theatres (276) and as a result they also owned the highest number of surgical beds.

When it comes to human resources, doctors play a central role in ensuring the success of especially private hospitals; they are the decision makers and indirect sellers of hospital services. An annual report on Medi-Clinic (Matsebula & Willie, 2006:165) stated that an estimated 7 000 medical specialists work in the private sector as compared to 4 000 medical specialists employed in public hospitals. Of the 4000 medical specialist in the public sector, some also practise in the private sector under a limited private practice (LPP) scheme

allowed by the state (Council for Medical Schemes, 2007a). In an annual report by Netcare (2006), it was reported that there was a shortage of nurses in the private sector, and this was a serious constraint and a risk factor limiting the industry's potential growth (Netcare, 2006:23).

The shortage of nurses also reported by the Hospital Association of South Africa (HASA) makes it difficult for private hospitals to contain costs since the biggest component of cost is staff costs, which were estimated to be as high as 77% of the total costs (Schussler, 2006:166). Khanyile (2007) reported further that the shortage of nurses also influences the cost because their salary increases were always higher than the inflation rate.

The private health care sector largely serves populations covered by medical schemes, although there is growth in other non-medical scheme businesses particularly from the self-pay market as quoted (Matsebula & Willie, 2007:166) in Council for Medical Schemes. HASA Health Annals estimated an annual turnover of the private health care sector industry at R175 billion, this being higher than the total amount spent by medical schemes in 2005 (approximately R16 billion) (Council for Medical Schemes, 2006).

Private hospital expenditure by medical schemes has increased since 1990 due to the decline in the quality of care in public hospitals coupled with the migration of specialists and general practitioners away from the public sector (Council for Medical Schemes, 2006). According to the press release of 30th August 2007, for an annual report for 2006/2007 for the Council for Medical Schemes assessing the financial performance of medical schemes during 2006, it was stated that the gross contribution income increased by 6.2% to R57.6 billion. Of this amount, R51.3 billion was paid out in benefits. This was an increase of 12.4% on the R45.6 billion paid out in the previous year (Council for Medical Schemes, 2007a:2).

The expenditure on hospital services accounted for R17.9 billion, or 35% of the total benefits paid to providers. This was an increase of 13.6% on 2005 data and private hospitals were paid R274 million. Payment to medical specialists accounted for R11 billion or 21% of benefits paid in 2006. General practitioners received R4.4 billion, or 8.6% of total benefits paid. This was an increase of 17.2% compared with 2005 (Council for Medical Schemes, 2007b:15).

According to the South African Health care report (Adler, 2008), the private health care costs have hardly been contained. For example, between 1996 and 2001, the cost of specialty care increased by 43%, and the cost of hospital care rose by 65%. The number of South Africans who lack health insurance - the bulk of the population - has continued to grow rapidly, consumer-driven health plans have done too little to address SA's most pressing health problem: HIV/AIDS (Taylor *et al.*, 2007: 446). The total number of membership of all

medical schemes according to the Actuarial Society of SA (da Silva & Wayburne, 2008:39) was about 7 million (approximately 16% of the SA population) beneficiaries since 1998. For HIV/AIDS patients, many medical schemes covered only very urgently needed ARV treatment as part of their medical savings and stopped providing treatment when funds were exhausted. In January 2005, all medical schemes had to provide PMBs for HIV/AIDS for their members, according to the amendment of the Medical Schemes Act of 1998 (131/1998) (da Silva & Wayburne, 2008:40).

At the opening address by the then Minister of Health, Dr. Tshabalala-Msimang, at the private Health Sector Indaba, in 2007 (Tshabalala-Msimang, 2007) it was reported that the minister stated strategies that aimed at transforming the private health sector, including issues of costs, affordability and transparency. It was also emphasised that the private health care sector, also needed a coherent regulatory framework to ensure that it operated in the best interests of all citizens of SA not merely its shareholders. Of major concern was the significant increase in expenditure on private hospitals from R8 billion in 1997 to R17.7 billion in 2006/2007 (Department of Health, 2008a). This represented a 121% increase in only 10 years, furthermore, the specialist costs increased from R5 billion in 1997 to R11 billion in 2006/2007, an increase of 120%. Therefore measures had to be discussed that needed to be adopted by both government and the private sector to ensure transparency.

A report from the Health Systems Trust (2008) on Health Statistics indicated that health expenditure in terms of National GDP that is spent on health care in the private sector in SA was 5.0% in 2007 as compared to 3.5% in the public sector. Then a ratio of private to public sector per capita health expenditure was 5.5% for 2006/2007 and 5.3% for 2007/2008 (Anon, 2008:45). Reports from the National Treasury, Health Systems Trust and The Valley Trust (Blecher *et al.* 2008:181) stated that the public sector funding for health services comprised of 3.5% of the GDP and 14% of total government expenditure, excluding interest payment in 2008/2009. Total health expenditure on non-hospital PHC services by the public sector per person without medical aid coverage increased from R256 billion for 2006 to R302 billion in 2007 (Department of Health, 2008a).

In 2007, a programme called Council for Health Services Accreditation of SA (COHSASA) was introduced in SA to assist hospitals to improve patient safety. COHSASA is the only local health care accreditation organisation in SA that has been accredited by the International Society for Quality in Health Care (ISQua) (COHSASA, 2007). Its first accreditation was from 2002 to 2006 and it second from 2006 to 2010. According to Keegan (2009), this programme is used by the National Department of Health, provincial health services and private hospitals, as a surveillance tool. A recent report from COHSASA hospital accreditations indicated that only 66 facilities hold COHSASA accreditation in SA (COHSASA, 2007). A report from the

Hospital Association of SA (HASA) stated that though the majority of private hospitals were not enrolled in the COHSASA programme, both Medi-Clinic and Netcare owned hospitals have undergone the International Organisation for Standardisation (ISO) quality accreditation and were awarded the International Healthcare Accreditation and Quality Unit (HAQU) as well as ISO 9001: 2000 certificate (HASA, 2008).

1.2.2 Prevalence of HIV infection

SA has the sixth highest prevalence of HIV-positive people in the world, with an estimated 5.7 million (18.8% of the population) living with HIV in 2007 (WHO/UNAIDS, 2008a:4; UNAIDS/WHO, 2008:215; The Henry J. Kaiser Family Foundation, 2007). The mid-year population estimates for 2008, reported the estimated overall HIV-prevalence rate to be approximately 11.0% with HIV-positive population to be approximately 5.35 million in SA (Statistics SA, 2008:3). According to the Joint United Nations Programme (UNAIDS) on HIV/AIDS 2008 Report, on the Global AIDS epidemic, it was reported that almost 33 million people were now living with HIV/AIDS worldwide, with 25 million people having died of HIV-related causes since the beginning of the epidemic (WHO/UNAIDS, 2008a:5).

According to The 2008 Global report on the HIV epidemic emphasized that the global percentage of adults living with HIV has been leveling off since 2000 (UNAIDS/WHO, 2008: 212). According to the report, in 2007 there were 2.7 million new HIV infections and 2 million HIV-related deaths. The rate of new HIV infections fell in several countries, but globally these favourable trends were at least partially offset by increases in new infections in other countries. In 14 of 17 African countries with adequate survey data, the percentage of young pregnant women (ages 15–24 years) who were living with HIV has declined since 2000-2001. In seven countries, the decrease in infections equalled or exceeded the 25% target decline for 2010 set out in the *Declaration of Commitment*. Sub-Saharan Africa remains the region most heavily affected by HIV, accounting for 67% of all people living with HIV and for 75% of AIDS deaths in 2007 (UNAIDS, 2008a:30).

An estimate of 320 000 people died of AIDS-related deaths in SA during 2005. In June 2007, Statistics South Africa (Noble, 2007) published a report on "Mortality and causes of death in SA" which revealed that the annual number of registered deaths rose by a massive 87% between 1997 and 2005 among those aged 25 to 49 years. SA is regarded as the most severely affected with the HIV epidemic in the world (AIDS Foundation SA, 2009; Pettifor *et al.*, 2005:1531).

A report from HIV/AIDS news stated that by 2010 HIV/AIDS would drive up the cost of health services in SA, and in 2007 the country's public health sector became strained as a result of the large numbers of HIV-positive people who developed AIDS-related illnesses. According to the 2006 AIDS epidemic update, in SA

some 5.5 million (4.9 million–6.1 million) people, including 240 000 (93 000 – 500 000) children younger than 15 years, were living with HIV in 2005 (UNAIDS, 2006:6). HIV data gathered in the country's extensive antenatal clinic surveillance system suggest that HIV prevalence has not yet reached a plateau. Although the exact impact of the epidemic on South Africa's health infrastructure was unknown by 2005, HIV/AIDS patients accounted for 60% to 70% of hospital expenditure, and while the demand for care increased, the country's supply of health workers decreased (Department of Health, 2006:10).

Families and households in rural SA face the adverse demographic, social and economic consequences of the severe HIV epidemic (Hosegood *et al.*, 2007:1249). This is supported by Welz *et al.* (2007:1468) who indicated that in 2003/2004, the prevalence of HIV in adults (15-54 years) in areas of rural KwaZulu-Natal was 23%, and households had experienced multiple HIV-related illness and AIDS deaths of their own members, and extended families. The national average of HIV-positive women attending antenatal clinics in 2006 was 30.2%, with KwaZulu-Natal having the highest prevalence at 39.2% followed by Mpumalanga at 34.8% (AIDS Foundations SA, 2009; Department of Health, 2006:10). The 2007 national HIV prevalence estimates were at 28% (CI: 26.9% - 29.1%), representing a possible 1.1% reduction in HIV prevalence from 2006 to 2007 (Department of Health, 2008b:14).

The South African provincial HIV prevalence estimates as per 2006 to 2007 report indicated a decrease in the prevalence in KwaZulu-Natal from 39.1% in 2005 to 37.4% in 2007 and an increase from 30.3% in 2005 to 33.5% in 2007 for the Free State. In 2008, the KwaZulu-Natal provincial HIV prevalence amongst 15-49 year antenatal women was 38.7% (95% CI: 37.2%–40.1%). KwaZulu-Natal has consistently recorded the highest prevalence since 1990 (Department of Health, 2008b:14; Statistics SA, 2008:5)

Estimates released in the National and Provincial Indicators for 2006 by Dorrington *et al.* (2006:10) indicated that the prevalence of HIV/AIDS was higher for women than men for the 15 to 34 age group, while it was higher for men in the older age groups. Among women, the rate was the highest (at 32.5%) for the age group 25 to 29 years. Among men, the rate peaks at slightly older ages, with 26.5% of those aged 30 to 34 years. According to Johansson (2007:1616) many poor South Africans do not have access to ARVs, thus AIDS-related deaths are expected to peak at ages 30 to 40 years.

According to the latest report from the National Department of Health, SA the highest HIV prevalence of 38.7% (CI: 37.2%–40.1%) in 2008 was still seen in the province of KwaZulu-Natal and the lowest estimate of 16.1% (CI: 12.6%–20.2%) was noted in the Western Cape Province. Free State, Mpumalanga and the Western Cape provinces showed a slight increase in HIV prevalence, while KwaZulu-Natal, North West (which had prevalence above 30%) Northern Cape and Limpopo provinces remained static. Gauteng province

has shown a tendency towards a decrease, although this was not statistically significant. Mpumalanga province was the only province in the country that continued to show some evidence of an increase in HIV infection from 32.1% in 2006 to 34.6% in 2007 to 35.5% in 2008 (National Department of Health, 2009:9).

The 2008 report on the global AIDS epidemic gave the estimated number of people living with HIV for 2001 and 2007 in the top 10 countries in Africa as shown in Table 1.1. The estimated number of people living with HIV in East Asia, Oceania, South Asia, Europe, Western Europe, North America, Caribbean and Latin America is shown in Table 1.2 (UNAIDS/WHO, 2008:219).

It is problematic to obtain accurate statistics on the number of children orphaned as a result of AIDS. According to UNAIDS/AIDS report, if orphans are defined as children under the age of 17 years whose mothers have died, then there were 1 200 000 orphans living in SA by the end of 2005 (AIDS Foundation South Africa, 2009; UNAIDS/WHO, 2006:1). Based on the Department of Health study done in 2006, an estimate of 15.9% of all South Africans over 2 years old was reported to be living with HIV in 2005. According to the 2008 report, the HIV prevalence per age among women under the age of 25 years has remained stable over the past three years and it is in agreement with the total national HIV prevalence trend. The HIV prevalence estimates in the older age groups above 30 years, showed a tendency towards an increase from 30.7% in 2006 to 40.4% in 2008 (National Department of Health, 2009:8). This could be a reflection of AIDS-related mortality beginning to relent in this particular age group due to the provision of ARV treatment.

Table 1.1: Estimated number of people living with HIV in Africa (UNAIDS/WHO, 2008:214)

Country	**Adults and Children 2007**	**Adults and Children 2001**	**Adults (15+ years) 2007**
	Estimate	Estimate	Estimate
Global	***33 000 000***	***29 500 000***	***30 000 000***
Cameroon	540 000	530 000	500 000
Ethiopia	980 000	920 000	890 000
Mozambique	1 500 000	1 000 000	1 400 000
Nigeria	2 600 000	2 200 000	2 400 000
SA	5 700 000	4 700 000	5 400 000
Sub-Sahara	**22 000 000**	**20 400 000**	**20 000 000**
Tanzania	1 400 000	1 400 000	1 300 000
Uganda	940 000	1 100 000	810 000
Zambia	1 100 000	940 000	980 000
Zimbabwe	1 300 000	1 900 000	1 200 00

Table 1.2: Estimated number of people living with HIV in East Asia, Oceania, South Asia, Europe, Western Europe, North America, Caribbean and Latin America (UNAIDS/WHO, 2008:219)

	Adults and children 2007	**Adults and children 2001**	**Adults (15+ years) 2007**
Country	**Estimate**	**Estimate**	**Estimate**
Belarus	13 000	13 000	13 000
Brazil	730 000	660 000	710 000
China	700 000	470 000	690 000
Haiti	120 000	98 000	110 000
India	2 400 000	2 700 000	2 300 000
Italy	150 000	140 000	150 000
Papua New Guinea	54 000	10 000	53 000
United States of America	1 200 00	1 000 000	1 100 000

According to the Joint United National Programme on HIV/AIDS, in Sub-Saharan Africa, young people (particularly young women) continue to be one of the population groups at greatest risk for HIV infection (UNAIDS, 2006:8). Based on the wide range of data, including household and antenatal studies, UNAIDS/WHO (2007:8) in mid-2006 published an estimate prevalence of 18.8% in those aged 15 to 49 years at the end of 2005. HIV prevalence among 15 to 19-year-old women appears to be stabilising at around 15% whereas in the 20 to 24-year-old age group the prevalence increased from the 2002 levels to 30%. The highest prevalence rate was observed in the age group 25 to 29 years (35.4%). Lower prevalence rates (15.8%) were observed in teenagers (women under 20 yrs) (Makubalo *et al.*, 2004:8). The latest report of 2008, revealed that HIV prevalence in 2008 stood at 31.1% in 20 to 24 year group as compared to 31.5% in 2007 and 31.7% in 2006 (National Department of Health, 2009:5).

Another survey reported that among females, HIV prevalence is the highest in those between 15 and 49 years old; while among males, the peak is in the age group 20 to 64 years (Statistics South Africa, 2008:6). According to these results, males aged 15 to 49 years old (58%) are less likely to be infected than females in the same age group (11.7% in men versus 20.2% in women).In mid-2007, following the latest antenatal survey, the Department of Health, in collaboration with UNAIDS, World Health Organisation (WHO) and other groups, published an updated estimate of 18.34% prevalence in people aged 15 to 49 years old in 2006.

This equates to around 5.41 million people living with HIV in 2006, including 257 000 children (Department of Health, 2007:9).

1.2.3 HIV and AIDS: One of the challenges faced by the private health care sector in SA

The high level of the HIV epidemic had an impact on the private health care sector in SA especially on medical schemes, the major stakeholders in the private health care sector, as well as the beneficiaries. The high prevalence of HIV infection in the younger age group had an effect on reducing the implicit age cross-subsidies within a medical-scheme contribution factor (da Silva & Wayburne, 2008:36).

The Medical Schemes Act (131/1998) which was implemented on 1 January 2000, introduced, *inter alia*, community rating, guaranteed acceptance and PMBs. Then a Risk Equalisation Fund (REF) was also established to make sure that all medical-scheme beneficiaries paid the same industry community rate. Medical schemes had to choose to manage HIV/AIDS by introducing HIV disease management programmes for their members by introducing PMBs that had to be paid in full without co-payment or deductibles. In January 2000, the regulation stipulated that medical schemes had to provide treatment for HIV-related opportunistic infections and the costs of hospitalisation as part of the PMBs. Thereafter, as from January 2005, antiretroviral treatment (ART) was included as part of the PMBs (da Silva & Watburne, 2008:41).

The critical role of the private sector is the battle against HIV and AIDS in the workplace. In a conference on HIV/AIDS held in Gauteng on 5 and 6 November 2008, the private sector strategy was of zero tolerance to better respond to the pandemic, including zero tolerance for new infections, zero tolerance for AIDS deaths, zero tolerance for babies born with HIV, and zero tolerance for discrimination (Department of Health, 2008b:34). Reports from Health Systems Trust, Health Economics Unit - University of Cape Town and Aid for AIDS (Stevens *et al.* 2008:202) stated that there are some 100 000 patients receiving HIV and AIDS care within disease management programmes in the private health care sector and approximately 67 000 are currently receiving HAART.

1.2.4 Risk factors for HIV infection in SA

In a survey conducted by Pettifor *et al.* (2005:1532); the following were identified as risk factors for the high prevalence of HIV among the general population in SA

- High-risk and unsafe sexual behaviours (Eaton *et al.*, 2003:149).

- Food crises attributable largely to the HIV/AIDS epidemic leading to starvation (de Waal & Whiteside, 2003:1234).
- Sexually transmitted diseases that influence the probability of HIV transmission, including non-communicable diseases (Bourne *et al.*, 2002:157).
- Multiple lifetime sexual partners or older partners (Morrison *et al.*, 2001:S61).

These authors recommended programmes for youth, including lovelife that would continue to promote partner reductions and consistent condom use. Additional recommendations included the addressing of contextual factors affecting young women, to implement behavioural change (for example, poverty, gender inequalities, and social norms regarding HIV testing) and strengthening interventions that reduce the probability of HIV transmission, such as improved access to STI treatment.

Another important risk factor that has been researched is gender-based violence and gender inequality as essential determinants of women's HIV risk, both worldwide and within Sub-Saharan Africa (Jewkes *et al.*, 2003:125). Another study done in SA postulated that women with violent or controlling male partners are at risk of HIV infection, because abusive men are more likely to have HIV and impose risky sexual practices on partners (Dunkie *et al.*, 2004a:1415).

Other risk factors as stipulated by Da Silva and Wayburne (2008:50) include: Income and employment. Relatively poor people suffer from high risk of HIV infection for the following facts: poor women are being forced into sexual relationships for monetary reasons as stated by Dunkie *et al.* (2004b:1581). Furthermore, the poor are less likely to be educated about HIV control and its transmission (Gregson *et al.,* 2001:1). Early coital debut as stated by Pettifor *et al.* (2004: 1435) is a significant predictor of prevalent HIV infection.

1.2.5 Treatment, care and support for people with HIV/AIDS

WHO estimated in June 2005, that 4.7million people living in Sub-Saharan Africa were in urgent need of ART (UNAIDS/WHO, 2005:13). Several initiatives to achieve large scale delivery of ART to people infected with HIV especially in resource-limited countries were launched. Until 2003, treatment, care and support, except for those on medical aid or with private sponsorship, meant treatment for ongoing opportunistic infections, palliative care and bed care. The prospect of life-prolonging treatment as opposed to treatment to relieve symptoms is still remote to the majority of those infected. There have been huge numbers of people dying from AIDS due to inaccessible treatment (AIDS Foundation South Africa, 2005). According to the WHO (2005a, VII), an estimation of 250 000 to 350 000 deaths were averted in 2005 in low-and middle-income countries as a result of widened access to HIV treatment.

In the private sector, much of the focus on HIV/AIDS care has been on the provision of HAART and the private sector provided this care more than the public sector. Another goal in the private sector was to partner with other sectors in society to reduce the sexual transmission of HIV and to scale up prevention programmes for HIV positive people (Stevens *et al.*, 2008:202). HIV/AIDS in the private sector is catered for by the medical schemes in terms of the Medical Schemes Act (131/1998) under "PMBs" related to HIV infection (McLeod *et al.*, 2003:77).

1.2.6 HIV/AIDS management in the public sector: ARV programme

The most significant development in the HIV/AIDS struggle in SA was the decision taken by Government in 2003 to provide HIV care, management and treatment (National Department of Health, 2004:6). The ARV rollout has been happening at different rates, on different scales and with different degrees of commitment and success from district to district and province to province. The number of patients that were on ARV treatment in SA was released for the first time in January 2005. The statistics showed that about 29 000 people were on ARV treatment at more than 113 public hospitals with 8 467 in KwaZulu-Natal; 10 000 in Gauteng; 515 in Northern Cape; and nearly 2 800 in North West Province. Mpumalanga had almost 1 000 patients by the end of December, Free State 945 and Limpopo only 729 and the Western Cape nearly 6 200 (AIDS Foundation South Africa, 2005).

A report entitled, "*Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector*", released by the WHO, United Nations Children's Fund (UNICEF) and Joint UN Programme on HIV/AIDS (UNAIDS), stated that one of the most notable achievements in SA, was that the number of patients undergoing ARV treatment almost doubled, from 458 951 to 700 500, between 2007 and 2008 (South Africa, 2009a).

The South African strategic plan for HIV and AIDS for 2000-2005, was to provide a comprehensive framework in response to the epidemic by providing a comprehensive package of care by providing ART to patients in the public sector. Standard National ART guidelines were formulated for both adults and children (National Department of Health, 2004:3; National Departmeny of Health, 2005:4). The purpose of the guidelines was to set standards as the basis for the use of ARV drugs in SA on which training- and support-programmes were to be based. The guidelines are reviewed periodically to ensure that there is continuity in the provision of quality of care.

1.2.7 HIV/AIDS management in the private sector

In May 1998, the South African private health care sector launched Aid for AIDS (AfA) initially as a small HIV disease management programme (DMP) to manage the outpatient benefits contracted to medical schemes (Regensberg & Makiwane, 2009:6). Other HIV management solutions included the development of corporate DMPs for companies who wished to make treatments available for uninsured employees and public sector initiations. According to AfA Clinical Guidelines, the standard treatment guidelines for the start of ART in adults in the private sector are as follows: the patient must be ready for treatment and the patient who has WHO stage 4 condition (refer to Section 2.3.2.1.1) or other serious morbidity or two CD4 counts less than 350 cells/mm^3 done at least every six weeks (Regensberg & Makiwane, 2009:41). In the private sector, HIV/AIDS is managed through PMB treatment plans for those patients who are beneficiaries of medical schemes. The PMBs for HIV/AIDS as from January 2000 included only the treatment and management of opportunistic infections and localised malignancies (McLeod *et al.,* 2003:78). Then the 2002 regulation, which came into effect on 1 January 2003, extended the PMBs for HIV to include a further package of benefits like

- voluntary counselling and testing;
- treatment for tuberculosis;
- sexually transmitted infections and opportunistic infections;
- prevention of mother-to-child transmission (MTCT) of HIV; and
- post-exposure prophylaxis (PEP) following sexual assault.

Then as from 1 January 2005, ART was included as part of PMBs (da Silva & Wayburne, 2008:41).

1.2.7.1 Council for Medical Schemes in SA

The Council for Medical Schemes is a statutory body established by the Medical Schemes Act (131/1998) to provide regulatory supervision of private health financing through medical schemes (Council for Medical Schemes, 2009b). The Council for Medical Schemes fulfils a number of statutory objectives that include the following Medical Schemes Act (131/1998) and Pearmain (2000:186):

- To protect the interests of medical schemes and their members.
- To monitor the solvency and financial soundness of medical schemes.
- To control and coordinate the functioning of medical schemes in a manner that is complementary to the national health policy.
- To investigate complaints and settle disputes in relation to the affairs of the medical schemes.
- To collect and disseminate information about private health care in SA.
- To make rules with regard to its own functions and powers.

- To make recommendations to the Minister of Health on criteria for the measurement of quality and outcomes of the relevant health services provided for by medical schemes.

1.2.7.1.1 Medical schemes in SA

The Council for Medical Schemes supervises an important industry namely the medical schemes environment. A report of the audit committee (Moyo, 2007:49) of the Council for Medical Schemes annual report for 2006/2007 stated that there were about 124 medical schemes in SA in 2006 (41 open and 83 with restricted membership) with around 7.1 million beneficiaries, which is approximately 16% of the South African population. These schemes have a total annual contribution flow of about R57.6 billion (Council for Medical Schemes, 2008a:17). The total number of principal members of registered medical schemes increased by 6.2% to 2 985 350 in 2006. In addition, the number of dependants rose by 2.9% to 4 141 993, resulting in the number of beneficiaries increasing by 4.3% to 7 127 343. Open schemes registered a 4.7% increase in the number of principal members, while membership of medical schemes rose by 9.7% (Council for Medical Schemes, 2008a:17). According to the Medical Schemes Act (131/1998), open schemes are accessible to any individual as opposed to a restricted membership scheme meaning that a medical scheme has rules that restrict the eligibility for membership by reference to:

- employment or former employment or both employment or former employment in a profession, trade, industry or calling;
- employment or former employment or both employment or former employment by a particular employer, or by an employer included in a particular class of employers; and
- membership or former membership or both membership or former membership of a particular profession, professional association or union.

1.2.7.1.2 Membership of medical schemes

In an annual report of 2007/2008 (Willie *et al.*, 2008:2) a synopsis of findings by the Council for Medical Schemes was given, and it was reported that in 2007 the number of beneficiaries increased by 5.0% to 7 478 040. Furthermore membership of restricted schemes grew by 21.7%, and this growth attributed to the Government Employees Medical Scheme (GEMS) increasing its membership by more than 300.0% from 2006. The ratio of dependants to active members remained unchanged at 1.4 for 2007. The pensioner ratio decreased from 6.3% to 6.2%. The average age of beneficiaries as per report (Willie *et al.*, 2008:2) decreased from 31.6 years in 2006 to 31.4 years in 2007.

The contributions collected from members by the medical schemes increased by 12.3% to R64.7 billion, while the claims that medical schemes paid on behalf of their members rose by 10.2% to R56.3 billion from R51.1 billion in 2006. The percentage of contributions that medical schemes spent on claims was slightly lower. In 2007 medical schemes spent on average 86.0% of contributions on claims, as compared to 88.0% paid in 2006, this could have been to a younger member profile contributing to the lower claims (Willie *et al.*, 2008:5).

1.2.7.1.3 Age distribution of beneficiaries

In a review of operations by the audit committee on medical schemes in 2006, (Moyo, 2007:49) the age distribution of beneficiaries was high in the age range 30 to 50 years, with coverage in the 20 to 29 year group being lower than the other age groups. The 2006/2007 annual report for the Council for Medical Schemes (Moyo, 2007:49) indicated that the number of beneficiaries in all age groups increased in 2006. Marginal increases were recorded in the 40 to 44 age group and for those aged 60 years and older. The average age decreased to 31.6% from 31.7% in 2005.

1.2.7.1.4 Gender distribution of beneficiaries

The gender distribution of beneficiaries as reported by the audit committee (Moyo, 2007:50) was such that there were more male than female beneficiaries in the under-20 year group. However, the trend changed in that there were more females in medical schemes from the age of 20 years and older. As a result, there were proportionately more female than male beneficiaries. Furthermore female beneficiaries were also generally older than males; the average age of female beneficiaries being 31.6 years while for males it was 30.9 years.

1.2.7.1.5 Financial performance of medical schemes

According to the annual report 2007/08 of the Council for Medical Schemes (2008a:17), the expenditure was such that of the total amount spent on health care, R20.2 billion (36.0%) was paid to hospitals. Expenditure on private hospitals increased by 12.5% to R19.9 billion in 2007. The number of beneficiaries admitted to private hospitals increased to 180 per 1 000 beneficiaries from 171 per 1 000 in 2006. Payments to medical specialists accounted for R21.2 billion (21.7%) of benefits paid, representing an increase of 11.0% on 2006. General practitioners were paid R4.3 billion (7.7%) of the total benefits paid, representing a decrease of 1.5% on 2006. Of the total amount spent on health care in 2007, medical schemes paid R9.4 billion (or 16.7%) on medicines dispensed by pharmacists and providers other than hospitals. This was an increase of 8.2% as compared to R8.7 billion spent in 2006.

In the past, medical schemes were (and still are) the main means of financing private health care, although 84% of the South African population was not covered by medical aids, as members of medical schemes were (and still are) predominantly from high income groups, the white population, and formally employed persons (Thom, 2001). Since medical schemes were by law non-profit organisations, there was the tradition of cross-subsidy operating within medical schemes. This has resulted in the more traditional employment based medical schemes losing their younger members to commercial funds offering risk-rated premiums, with resulting steep premium increases by as much as 50% for the elderly and sick at the expense of young, healthy members. According to a report of the Pharmaceutical Industry Association of South Africa (PIASA), of the total benefits paid by medical schemes in 2006, 16.9% was spent on medicines (PIASA, 2008).

1.2.7.2 Reforms for medical schemes

In January 2000, one of the reforms for medical schemes was the introduction of a minimum package of benefits. This was introduced to be provided by all schemes. Annexure A of the Regulation to the Medical Schemes Act (131/1998) defined the PMBs in terms of exactly 270 diagnosis-treatment pairs (McLeod, 2005:151). The PMBs are a legislated set of benefits that each registered medical scheme is compelled to offer as part of each benefit option. The benefits in this package must be paid in full, without co-payment or deductibles. If a beneficiary chooses to use a provider who is not a 'designated service provider', then a co-payment becomes payable. The PMB package includes non-discriminatory cover for hospital and outpatient services (da Silva & Wayburne, 2008:40; McLeod, 2005:151; McLeod *et al.*, 2003:79; Pearman, 2000:196). These PMBs have to be provided in at least one network setting, and diagnosis and treatment must be covered in full from pooled funds, without financial limits or co-payments.

According to the 1999 Regulation of the Medical Schemes Act (131/1998), the objective of specifying a set of minimum benefits as stated by the Actuarial Society of South Africa (McLeod, 2005:151) was: "*to avoid incidents where individuals lose their medical scheme cover in the event of serious illness and the consequent risk of unfunded utilisation of public hospitals; and to encourage improved efficiency in the allocation of private and public healthcare resources*". Therefore on 1 July 2000, the Council for Medical Schemes began a process concerned with the implementation of PMBs and addressing some of the concerns identified such as the following (Council for Medical Schemes, 2009c:1; Council for Medical Schemes, 2008b:6):

- The limited availability of services at public hospitals.
- Problems with billing and fee structures in public hospital facilities.
- The ambit of the PMBs.

- Understanding of clinical treatment protocols and policy issues, for example, whether infertility treatment at public hospitals was, and should be, covered as a PMB and how HIV/AIDS should be managed as a PMB.
- Additional financial risk to medical schemes as a result of the minimum benefits and how medical schemes were managing this risk.
- Administrative problems experienced by medical scheme as a result of the PMB package.

1.2.7.3 Implementation of PMB package

PMBs surfaced to avoid hardships for patients who could not be accommodated in public hospitals and whose medical schemes had refused to pay private hospital rates in a public hospital, for example in cases where the private hospital was full, then such patients could be accommodated in a public hospital providing services but at public hospital rates. In addition to that PMB was implemented since private hospitals are not subsidised by the tax payer; they could not afford to treat patients at public hospital rates (Department of Health, 2008b:2).

Therefore a circular (Circular 3 of 2000) was issued by the Registrar of Medical Schemes to medical schemes stating that if patients could not obtain minimum benefits services in public hospitals they had to be accommodated in private hospitals at private hospital rates (Council for Medical Schemes, 2009c:2). The PMB is a hospital-based package, meaning that it is biased against outpatients, ambulatory care and the control and management of chronic health conditions before hospitalisation became necessary (Council for Medical Schemes, 2009c:2).

1.2.7.4 Conditions of implementing PMBs in SA

PMBs is a list of 270 conditions / groups of conditions (as listed in Annexure A of the Medical Schemes Act (131/1998) and 27 chronic diseases that all medical schemes are compelled to cover as stated by the Council for Medical Schemes (2008c:2) PMBs have the following advantages as stipulated by Umed (2005); Ingwehealth (2005) and Polmed (2005) medical schemes, amongst others:

- It covers all members, regardless of the option chosen.
- There are unlimited chronic medicine covers.
- Benefits are covered at 100% of cost.
- No levies and co-payments are applicable.

- Should the medical benefits of a member be depleted and his or her diagnosis, care and treatment fall under the PMBs, the scheme will still cover the cost in full, without co-payments.

In the regulations of 4th November 2002, substantial clarifications of the PMB requirements were provided such as defined emergency procedures and the need for designated service providers (DSPs). For example, medical schemes could make use of managed care techniques such as pre-authorisations, the development of formularies and the use of a restricted network of providers in order to ration care. Co-payments could be levied if a member chose to use a provider who is not the contracted DSP (Council for Medical Schemes, 2009b).

1.2.7.5 List of chronic diseases under PMBs

On 6th October 2003, the therapeutic algorithms for 26 chronic diseases previously identified (also referred to as the Chronic Disease List (CDL) was published (Taylor *et al.*, 2007:447). Diagnosis descriptions for the particular conditions were based on the *International Classification of Diseases Version 10 (ICD-10)* coding and the treatment was described as a stepwise approach to pharmacological management (Taylor *et al.*, 2007:447). The CDL includes 26 chronic disease PMBs, the most common conditions which represent 77% of all chronic conditions commonly seen in general practice and these include *inter alia* Addison's disease, Asthma, Bronchiectasis, Cardiac failure, Cardiomyopathy, Chronic Obstructive Pulmonary Disease (COPD), Chronic renal failure, Coronary artery disease, Crohn's disease, Diabetes insipidus, Diabetes mellitus types 1, Diabetes mellitus types 2, Dysrhythmias, Epilepsy, Glaucoma, Haemophilia, Hyperlipidaemia, Hypertension, Hypothyroidism, Multiple Sclerosis, Rheumatoid arthritis, Parkinson's Disease, Schizophrenia, Systemic lupus erythematous and Ulcerative colitis (Council for Medical Schemes, 2009c:2).

The compulsory ICD-10 coding by health care providers was implemented in the private sector on all medical accounts as from 1 July 2005 (Naude, 2008:25). By law, practitioners are required to include the ICD-10 code that applies to the relevant medical diagnosis for every single line item on a medical account since 1 July 2005. This should be used in conjunction with National Pharmaceutical Product Interface (NAPPI)-codes when medicine or stock is issued. The ICD-10 codes also ensure that the medical aid has the necessary information to route claims to the correct benefit categories for the patient's benefit options. This is particularly beneficial in the case of PMBs to ensure that these claims are funded via the medical scheme fund and not the day-to-day savings account of the patient (Naude, 2008:27).

Furthermore, a policy process to define and implement basic essential health care to be available in both the public and private sectors was formulated by the Taylor Committee (Taylor *et al.*, 2007:447). An example of

this link was the benefits in respect of HIV/AIDS. Initially the PMB for HIV/AIDS covered only opportunistic infections. Thereafter, the benefits were extended to cover mother-to-child transmission and rape prophylaxis once available in the public sector. As from January 2005, the medical schemes included ART in PMB, after the public sector had committed to the roll-out of an ART programme for the management of HIV infection (Taylor *et al.*, 2007:448). There are currently 27 chronic diseases on the CDL.

1.2.7.6 Management of chronic diseases under PMBs

The list of PMBs has been extended to cover all the common chronic diseases (Chronic diseases are now the major cause of death and disability worldwide). Non-communicable conditions, including cardiovascular diseases (CVD), diabetes, obesity, cancer and respiratory diseases, now account for 59% of the 57 million deaths annually and 46% of the global burden of disease (WHO, 2004:1). Relatively few risk factors – high cholesterol, high blood pressure, obesity and smoking – cause the majority of the chronic disease burden (WHO, 2005b:1).

Chronic diseases are managed through disease management, an intervention designed to manage or prevent a chronic disease using a systemic approach to care and potentially employing multiple treatment modalities (Ellrodt *et al.*, 1997:1687). In SA chronic diseases are managed using policy guidelines. Specific "treatment algorithms" (guidelines for appropriate treatment) have been gazetted for each chronic condition covered by PMBs to ensure standard quality treatment and protection from undue expenses. In this way limiting the costs of medicines provided for the management of chronic diseases listed under PMBs (Nicolosi & Gray, 2009:60).

1.2.7.7 PMB for HIV/AIDS

According to a report from the Health Systems Trust (Cameron, 2002) the Council for Medical Schemes had issued new draft regulations that significantly improved the protection of medical scheme members; stopping schemes from placing artificial barriers in the way of potential members; and stopping schemes from trying to avoid paying for chronic treatment like for HIV/AIDS. Therefore, a survey commissioned by the Council for Medical Schemes and conducted by the Centre for Actuarial Research (McLeod *et al.*, 2003) showed that the restrictions occurred through financial limits as opposed to 'deliberately-formulated inappropriate clinical protocols' for the management of the disease. Recommendations made by the Council for Medical Schemes were accepted by the Minister of Health to further expand the PMB package for ART, and therefore '*Operational Plan for Comprehensive HIV and AIDS Care, management and treatment for South Africa.*'

ART was included as part of the PMBs from 1 January 2005. According to the Council for Medical Schemes (2009c:2), PMBs for HIV/AIDS included:

- Diagnosis: HIV-infection and treatment included.
- HIV voluntary counselling and testing.
- Co-trimoxazole as preventive therapy.
- Screening, preventive therapy and treatment for tuberculosis.
- Diagnosis and treatment of sexually transmitted infections.
- Treatment of opportunistic infections.
- Pain management in palliative care.
- Prevention of mother-to-child transmission (MTCT) of HIV.
- Post-exposure prophylaxis following occupational exposure and sexual assault (da Silva & Wayburne, 2008:41).

1.2.7.8 Standard treatment guidelines for ART

In SA the treatment regulations specified that ART be provided according to "*National Guidelines*" applicable in the public health care sector. The Department of Health's 'National ART guidelines' set out the following criteria to assess readiness for commencing ART (National Department of Health, 2004:3):

- Medical criteria: CD4 cell count less than 200 cells/mm^3, irrespective of WHO stage, or WHO stage IV (refer to Section 2.3.2.1.1) irrespective of CD4 cell count.
- Willingness and readiness on the side of the patient to adhere to their medication regimen.
- Attendance at two screening visits and an ART commencement visit.
- Two drug regimens being made available for eligible patients (National Department of Health, 2004:6).

1.2.7.9 Review of terms of reference of PMBs

According to the Department of Health (2008c:2), a review on the terms of reference of PMBs is conducted every two years and it involves the Council for Medical Schemes, stakeholders, provincial health departments and consumer representatives. The review focuses specifically on the development of protocols for the medical management of HIV/AIDS. The purpose of the review is to identify any changes to the regulations that might be required in respect of PMBs to further the goals of improved access, quality and reduced costs in health care. The focus of the review will be to encompass the following as stated by the Council for Medical Schemes (2008c:3):

- Any shortcomings in the current set of PMBs and appropriate measures to address them.
- The PMBs that should accompany the implementation of the Risk Equalisation Fund.
- Any measures required to ensure the sustainability of any package of PMB.
- Identify specific measures required to ensure the cost-efficiency of selected PMBs.
- Clarify the relationship that should exist between PMBs and the public health system.

1.2.8 DDIs as a challenge faced in treating chronic diseases

Drug-drug interactions (DDIs) are an important, widely under-recognised source of medication errors, representing a significant opportunity cost for health care systems (Seden *et al.,* 2009:5). According to Miravitiles *et al.* (2002:329), treatments administered to patients with chronic diseases, especially when used in multiple combinations, are not free of interactions and side-effects that can potentially impair health–related quality of life. From the literature survey, DDIs have been established from drugs used to treat chronic diseases: Carter *et al.* (2004:424) in hypertension; Perucca (2002:25) in epilepsy; Harrigan *et al.* (2001:68) in type 2 diabetes mellitus; Strain *et al.* (2004:87) in psychotropic conditions, and O'Brien (1998:28) in HIV/AIDS. It is envisaged that in future not only will the PMBs be extended to chronic diseases, but also to certain acute treatments. Furthermore it is not unreasonable to expect that the PMBs may play an important role to control accessibility, availability and cost of medical treatment in future.

Patients receiving ARVs are susceptible to DDIs because they are administered a variety of drugs that could interact with each other. The co-administration of contraindicated drugs has been found to account for 5.2% of 209 hospital admissions in patients receiving ARVs in Baltimore (Rastegar *et al.*, 2006:933). According to Clarke *et al.* (2008:HS-3), DDIs are a serious complication of taking multiple drugs and account for 3% to 5% of all in-hospital errors, and these range from drug toxicities to therapeutic failures.

1.2.8.1 DDIs with ART

As access to ARV therapy expands in SA the potential for DDIs becomes increasingly important to prescribers (Cohen *et al.*, 2002:42). DDIs are often a serious complication of taking multiple medications and according to Leape *et al.* (1995:35) account for 3% to 5% of all hospital medication errors. The consequences of these DDIs vary, ranging from drug toxicities to therapeutic failures (Clarke *et al.* 2008:HS-3). DDIs are of a particular concern in patients infected with HIV who are receiving HAART, especially those on protease inhibitors (PIs) since they are at a greater risk of developing clinically significant drug interactions (Miller *et al.*, 2007:1379). According to De Maat *et al.* (2003:224), ARVs used in the treatment of HIV are often prone

to drug interactions because many of them are metabolised through the cytochrome 450 enzyme (CYP450) system.

Drug interactions are an important aspect of the use of medication that may endanger patients and may be avoided by more careful prescribing. According to Tucker *et al.* (2001:107), DDIs pose significant concerns for the pharmaceutical industry and during clinical practice. Information on the inconsistencies of DDIs has been documented in major compendia and as reported by Driesen *et al.* (2006:143), they are a major concern to physicians, pharmacists, drug utilisation review (DUR) programme operators and patients because there is a lack of clear guidelines regarding the management of DDIs. Inconsistent information about DDIs can cause prescribing problems, possibly increasing the incidence of morbidity and mortality. The need to reduce errors in the administration of prescription medications has focused attention on the prevention of DDIs.

Drug interaction issues continue to present a major dilemma for clinicians caring for patients whose management is complex such as those infected with HIV. The inherent possibility of a drug interaction is magnified by the multitude of drugs being administered in HAART. In addition, other classes of medications are used to alleviate side-effects, reduce toxicities associated with HAART, or to treat concomitant diseases. DDIs may result in toxicity, treatment failure, or loss of effectiveness and can significantly affect a patient's clinical outcome. Therefore an understanding of the fundamental mechanisms of HIV DDIs may allow for early detection or avoidance of troublesome regimens and prudent management if they develop (Krikorian, 2005:278).

1.2.8.2 Prevalence of DDIs between ARV drugs

Antiretroviral drugs used in HIV/AIDS possess a high potential for DDIs. Miller *et al.* (2007:1383) reported in a retrospective study on HIV/AIDS patients who were receiving ARV therapy, that clinically significant drug interactions were more prevalent among protease inhibitor (PI)-based than non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens ($p<0.001$), and these represented 54%. Pettifor *et al.* (2005:1527) reported on HIV prevalence stating that 15.5% of young women were more likely to be infected in comparison with their male counterparts with 4.8%.

1.2.8.3 Risk factors for DDIs in HIV/AIDS

The management of HIV/AIDS is achieved through the use of HAART, which consists of combination ARV treatment. Unfortunately ARV agents possess a high potential for DDIs between themselves and with other

drugs. Miller *et al.* (2007:1381) identified specific risk factors associated with clinically significant DDIs with ARV therapy. These risk factors included the following:

- Age older than 42 years.
- More than three co-morbid conditions.
- Treatment with more than three ARVs (excluding ritonavir used as a boosting agent), and treatment with a PI.

In another study, it was stated that metabolic abnormalities came to prominence when potent combinations of ARV therapy were introduced (Fitchenbaum, 2009:85). New regimens had to be introduced and substantial complexities existed in treating these disorders, and this was illustrated by complex DDI between lipid-lowering agents and ARVs (Fitchenbaum, 2009:85).

1.3 RESEARCH QUESTIONS

Based on the above literature, the following research questions were formulated:

- What is the composition of the South African health care system, and its challenges? (Refer to Section 1.2.1).
- What is the prevalence of HIV/AIDS in SA and other countries and its risk factors? (Refer to Sections 1.2.2 to 1.2.4).
- What is ARV treatment, care and support for people with HIV/AIDS like? (Refer to Section 1.2.5).
- How is HIV/AIDS managed in the public and private health sectors in SA? (Refer to Sections 1.2.6 to 1.2.7).
- What is the Council for Medical Schemes and its reforms in SA related ARV therapy? (Refer to Sections 1.2.7.1 to 1.2.7.2).
- What are Prescribed Minimum Benefits with specific reference to the PMB for HIV/AIDS in SA? (Refer to Sections 1.2.7.3 to 1.2.7.9).
- What are the challenges of DDIs in the management of chronic diseases with specific reference to HIV/AIDs management using HAART? (Refer to Sections 1.2.8 to 1.2.8.3).
- What are the different recommended management guidelines for HIV/AIDS in SA and other countries and the potential for DDIs in the recommended guidelines? (Refer to Sections 2.2.1 to 2.3.4.8).
- What is the importance of adherence to ART, its risk factors and strategies to enhance it? (Refer to Sections 2.3.5 to 2.3.5.3).

- What are DDIs and possible causes, the general incidence and prevalence of DDIs in clinical practice, what diseases and drugs that are at a high risk of adverse drug interactions? (Refer to Sections 2.4 to 2.8.2).
- What is the prevalence of prescriptions with potential DDIs in HIV/AIDS presented in a private health care setting in SA? (Refer to Sections 2.9 to 2.10.3).
- What are the pharmacological aspects of DDIs in ARV drugs in terms of clinical significance, risk factors and management? (Refer to Sections 2.11 to 2.12).
- What is the role of the pharmacist in preventing and managing DDIs in ART in clinical practice? (Refer to Section 2.13).
- What are the recommendations for preventing, controlling and management of possible DDIs between ARVs themselves and with other drugs prescribed to patients in different age groups in the private health care sectors? (Refer to Section 2.14).
- What are the recommendations for reducing DDIs between Ritonavir and other ARVs? (Refer to Section 4.5).
- What are the recommendations on the prescribing protocols for ARVs and management of potential DDIs between ARVs prescribed by different prescribers using PDDs in different age groups? (Refer to Section 4.6).

1.4 RESEARCH OBJECTIVES

The research objectives were divided into a general objective and specific objectives:

1.4.1 General research objective

The general research objective was to investigate the prevalence of prescriptions with potential DDIs between ARV drugs in a section of the private health care sector, utilising medicine claims data from PBM companies in SA

1.4.2 Specific research objectives

The specific research objectives of the *literature study* included the following:

- To investigate problems faced by the private health care that resulted in changes being made to the Medical Schemes Act (131/1998). (Refer to Sections 1.2 to 1.2.7.2).

- To study the implementation of PMBs, in SA with specific reference to the inclusion of HIV/AIDS, in the PMB. (Refer to Sections 1.2.7.3 to 1.2.8.3).
- To analyse different recommended management guidelines for HIV/AIDS in SA and other countries and the prevalence of potential of DDIs in the recommended guidelines. (Refer to Sections 2.2.1 to 2.3.5.3).
- To determine DDIs, different types, significance levels, dynamics and rating systems, and risk factors, with specific reference to HIV/AIDS. (Refer to Sections 2.4 to 2.9).
- To determine the risk factors and influence of DDIs in ARV therapy in HAART. (Refer to Sections 2.12).
- To investigate the role of pharmacists in detecting, controlling and preventing DDIs in clinical practice. (Refer to Section 2.13)
- To discuss the evaluation of Prescribed Daily Doses (PDDs) in the management of DDIs. (Refer to Sections 4.6 to 4.6.1).
- To determine the influence of PDDs on the prevalence of prescriptions with potential DDIs between ARVs prescribed by different prescribers in different age-groups. (Refer to Sections 4.6.2 to 4.7).

The specific research objectives of the *empirical study* were addressed in specific research articles as illustrated in Table 1.3.

Table 1.3: Specific research objectives of the empirical study addressed in different research articles

SPECIFIC RESEARCH OBJECTIVE OF EMPIRICAL STUDY	ARTICLE(S) IN WHICH IT WAS ACHIEVED (refer to Section 1.5.10)
To determine the prevalence of HIV/AIDS patients in the private health care sector in SA using medicine claims databases of two PBMs.	• **2008:** *South African medical journal* (**SAMJ**), 98(2):109 - 113. • **2008:** *International journal of pharmacy practice* (**IJPP**), 16:403 – 408. • **2008:** *Journal of clinical pharmacy and therapeutics,* (**J Clin Pharm Ther**) 33:393 – 400. • **2009:** *African journal of primary health care and family medicine* (**PHCFM**), 2009, 1(1): 1 – 6. • **2009:** *International journal of STD & AIDS* (**Int J STD AIDS**) (Date accepted for publication: 17th Aug. 2009). • **2009:** *Pharmacoepidemiology and drug safety* (**Pharmacoepidem Dr S**) (Submitted on 16th Oct. 2009)
To estimate the total number of ARV prescriptions and medicine items claimed through the PBM companies.	• **2008: SAMJ,** 98(2):109 - 113. • **2008: IJPP**, 16:403 – 408. • **2008: J Clin Pharm Ther**, 2008; 33:393 – 400. • **2009: PHCFM**, 1(1):1 – 6. • **2009: Int J STD AIDS** (Date accepted for publication: 17th Aug. 2009). • **2009: Pharmacoepidem Dr S** (Submitted on 16th Oct. 2009)
To determine the prevalence of prescriptions with potential DDIs identified between ARVs and other drugs as well as between ARVs themselves on a prescription in this section of the private health care sector.	• **2008: SAMJ,** 98(2):109-113. • **2008: IJPP**, 16:403 – 408.

Table 1.3: Specific research objectives of the empirical study addressed in different research articles (continued)

To investigate the prevalence of prescriptions with possible DDIs between ARV agents in different age groups.	• **2008: J Clin Pharm Ther**, 2008; 33:393 – 400. • **2009: Int J STD AIDS** (Date accepted for publication: 17th Aug. 2009). • **2009: Pharmacoepidem Dr S** (Submitted on 16th Oct. 2009
To determine the influence of Prescribed Minimum Benefits (PMBs) on the prevalence of prescriptions with potential DDIs between ARV agents and other drugs in a section of the private health care sector in SA.	• **2008: IJPP**, 16:403 – 408.
To analyse the prevalence of prescriptions with potential DDIs identified between ritonavir and other ARVs in a section of the private health care sector in SA.	• **2009: PHCFM**, 1(1):1 – 6.
To identify prescriptions with potential DDIs between ARVs and to determine whether PDDs can be used in the evaluation of these interactions in a section of a private health care sector in SA.	• **2009: Int J STD AIDS** (Date accepted for publication: 17th Aug. 2009).
To investigate the prevalence of prescriptions with potential DDIs between ARV drugs on prescriptions prescribed by general practitioners (GPs) and specialists (SPs) in SA and the evaluation of the prescribed daily doses (PDDs) of the interacting drugs.	• **2009: Int J STD AIDS** (Date accepted for publication: 17th Aug. 2009). • **2009: Pharmacoepidem Dr S** (Submitted on 16th Oct. 2009)
To formulate recommendations regarding management of level 2 DDIs between ARVs in clinical practice, referring to the recommended treatment guidelines	• **2008: SAMJ,** 98(2):109-113. • **2008: IJPP**, 16:403 – 408. • **2008: J Clin Pharm Ther**, 2008; 33:393 – 400. • **2009: PHCFM**, 1(1):1 – 6. • **2009: Int J STD AIDS** (Date accepted for publication: 17th Aug. 2009). • **2009: Pharmacoepidem Dr S** (Submitted on 16th Oct. 2009)

1.5 RESEARCH METHODOLOGY

1.5.1 Phases of the research project

The research project consisted of the following two phases:

- Literature study.
- Empirical investigation

1.5.1.1 *Phase one: Literature study*

The literature study was divided into two steps:

The first step includes a discussion on the South African health care system in terms of two systems: private and public. Thereafter, a description of the quality of health care, expenditures on health care and human resources followed and continued with a discussion on HIV and AIDS as a challenge faced by the private health care sector. The prevalence of HIV/AIDS in SA and other countries including the risk factors for HIV/AIDS in SA were discussed. Next the treatment, care and support for people with HIV/AIDS, plus management of HIV/AIDS with specific attention to the private sector in SA were explored. Then challenges faced by the private health care sector that led to the establishment of the Council for Medical Schemes in SA were discussed including the reforms for medical schemes that included implementation of the PMBs package. Thereafter the inclusion of HIV/AIDs in PMBs and management of HIV/AIDS according to PMBs conditions in private sector were focused on including terms of reference for PMBs in SA Finally a brief introduction of DDIs as a complication to HIV/AIDS management using HAART and risk factors for DDIs in HIV/AIDS was discussed.

The last discussion was on the recommended management guidelines for HIV/AIDS and DDIs in ARVs in Chapter 2. This chapter covered management of HIV/AIDS using different management systems. The South African ART guidelines both in public and private health care sectors were discussed, followed by the recommended ART guidelines in other countries showing similarities and differences to the South African guidelines. Thereafter a discussion on HIV/AIDS management in the private health care sector in SA was done followed by the potential for DDIs in ART guidelines. Adherence to ART, factors that influence it and strategies that enhance adherence were discussed. Then a final discussion was on the overview of DDIs in terms of concept, types, mechanisms, their dynamics and rating system, factors that place patients of developing clinically significant DDIs. Incidence and frequency of DDIs in clinical practice, including drugs and diseases that are prone to DDIs were discussed. Pharmacological aspects of DDIs in ARVs including risk

factors for DDIs between ARVs were also focused on. Then a final discussion followed on the role of pharmacists in preventing and managing DDIs between ARVs in clinical practice.

1.5.1.2 *Phase two: Empirical investigation*

The empirical investigation consisted of the following steps, namely:

- Selection of the research designs.
- The study populations and data sources.
- The selection and application of the criteria and measuring instruments for data analysis.
- Data analysis.
- Reliability and validity of the research instruments.
- Ethical aspects.
- Report and discussion of the results of the empirical investigation.
- Selection of the research articles.
- Conclusions and recommendations based on the results of the empirical investigation as well as the limitations of the study.

1.5.2 Research design

A non-experimental, quantitative, retrospective drug utilisation review method was used in order to obtain the essential outcomes and achieve the specific objectives for this research project. The study design is descriptive in nature.

The following aspects were used in the empirical study: pharmacoepidemiology and drug utilisation review.

1.5.2.1 Pharmacoepidemiology

Pharmacoepidemiology is the study of the use and effects of drugs in populations (Van Boxtel & Wang, 1997:205). It focuses on questions of pharmacodynamics, concentrating on clinical patient outcomes and on therapeutics (that is, appropriate use of drugs), and to a lesser extent on pharmacokinetics. Thus, pharmacoepidemiology applies the research methods of clinical epidemiology as stated by Martin (2005:99) (for example, randomised trials, cohort studies and case-control studies) (Strom, 1994a:15) to the content area of pharmacology (for example, determinants of beneficial and adverse drug effects, effects of genetic

variation on drug effect, dose-response relationships, duration-response relationships, clinical effects of potential DDIs, and effects of non-adherence).

Pharmacoepidemiology is an important tool for understanding and documenting the relationship between the use of drugs and adverse events, with side-effects being an important consideration for clinicians making treatment decisions (Kaufman, 2008:181). Pharmacoepidemiology was an important aspect to be considered in this study because it is an established subdiscipline of epidemiology that is concerned with estimating the efficacy, effectiveness and safety of pharmaceutical products (Briggs & Levy, 2006:1079).

In this study the safety of using ARVs was being evaluated by analysing potential DDIs that could occur between them. Furthermore the data used were electronic medicine records from medicine claims databases adding value to the popularity of pharmacoepidemiology as an important tool in research (Harpe, 2009:138).

1.5.2.2 Drug utilisation review

Drug utilisation review (DUR) is defined as the description of the patterns of drug use in specific populations (Bjornson as cited by Truter (1999:54). Spooner *et al.* (1999:1954) defined DUR as an introduction of educational or regulatory interventions to improve patterns of drug use consistent with accepted standards of appropriateness. Therefore this was a relevant aspect to consider in the empirical study of this project because one of the objectives of this study was to investigate the influence of the prescriber on the prevalence of prescriptions with DDIs between ARV drugs with specific reference to the age groups with the aim of establishing whether ARVs are being prescribed according to the recommended treatment guidelines.

Drug utilisation review studies can be either retrospective or prospective and quantitative. Retrospective studies as defined by Olson (2004:256) are when data are collected and analysed after the events of major interest (prescription, dispensing and use of drugs) have occurred. Strom (1994a:25) described retrospective studies as those in which patterns of drug use are determined after the drug has been dispensed. This was relevant for this research project because data were being extracted from medicine claims databases of PBM Companies. The data contained ARV prescriptions that had already been dispensed to the patients. For example a retrospective analysis in the treatment-experienced adults was done to find out any association between pharmacy medication refill-based adherence rates and CD4 count and viral-load responses (Townsend *et al.*, 2007:711).

Prospective studies are analytical studies designed to determine the relationship between and a characteristic shared by some members of a group. The researchers follow the population group over a period of time noting the rate at which a condition occurs. An example is a case-control study using exposure data that had been collected before the diagnosis of the disease (Strom, 1994a:25). This design was not used in the project because data required were ARV prescriptions already claimed from the medical schemes.

Quantitative drug utilisation studies as described by Lee and Bergman (1994:380) estimate drug - utilisation in populations by different demographic factors (such as age and sex) to identify areas of possible over-utilisation or under-utilisation. It was selected as an appropriate study method for this research project because one of the objectives of this study was to estimate the total number of ARV prescriptions and medicine items claimed through the PBM Companies, and to investigate the prevalence of potential DDIs between ARVs in different age groups.

1.5.3 Data sources and study population

1.5.3.1 Data sources

The data for the study were obtained from the medicine claims databases of two South African PBM companies, namely A and B. For security, ethical, and patient and provider identification reasons, the PBM companies are not identified by name. Database A is a medicine claims database of a PBM company that is an independent and specialised managed health care company. It offers clients a unique combination of high performance technology. It functions as a managed care organisation (MCO) appointed by a medical scheme to manage the complex issues around the authorisation and utilisation of CDL medicines. Furthermore, it offers solutions to uninterrupted access to pharmacies' database system, and provides instant responses to their requests. It acts as a link between health providers and medical insurers by managing medical benefits, in this instance specific medicine usage management benefits. It processes in the region of 80 000 transactions per day through a network of more than 3000 pharmacies and doctors and 20 medical insurances.

Database B, similar to database A, is a national medicine claims database of a PBM company. It has in place appropriate electronic and managerial procedures to safeguard and help prevent unauthorised access and maintain data security, including reference material and database for pharmaceutical companies. It provides a real-time auditing process to claims from pharmacies and service providers. During 2004 to 2006, the medical scheme administrators administered claims from 80, 60, and 36 medical aid schemes respectively. The different databases used to achieve the different research objectives and the different data that were collected and analysed from each are shown in Table 1.4. The two databases were chosen because it was

possible to collect relevant data that would provide information as related to the specific research objectives of the empirical study as stated in Section 1.4.2. Both databases are national medicine claims databases of PBM companies.

1.5.3.2 Study population

The general statistics of the two databases used in this study are presented in Table 1.4. As shown in Table 1.4 the general statistics employed were extracted from database A for years 2004 to 2006 and from database B for years 2005 to 2007.

Table 1.4: General statistics of databases A and B

Data	Database A			Database B			Total
	Year			Year			
	2004	2005	2006	2005	2006	2007	
Number of prescriptions	2595254	1621736	993804	8506355	9029912	8015535	**30762595**
Number of ARV prescriptions	43482	51613	47085	49995	81096	88988	**362259**
Number of patients	657 009	379 352	275424	1218358	1259099	911212	**3664039**
Number of patients on ARV treatment	9065	9290	8999	7664	10162	10061	**55241**

The following information on the dataset of database A was used during the analysis: (i) a specific code for the medical scheme (i.e. the specific medical scheme could not be identified), (ii) medical scheme member's number, (iii) dependant's number, (iv) prescription number, (v) date of dispensing the prescription, (vi) trade name of the medicine item, (vii) National Pharmaceutical Product Interface (NAPPI)-code (refer to Section 1.5.4.1), and (viii) number of the medicine items prescribed.

The following information was obtained from database B: drug's trade name, National Pharmaceutical Product Interface (NAPPI)-code (refer to Section 1.5.4.1), date of dispensing the prescription, prescription number, allocated identification numbers of patients' dependants, physicians, and pharmacies, number of the medicine items prescribed, number of days supplied, patient's gender, and patient's date of birth. Dummy

membership-, physician-, pharmacy- numbers (randomly allocated by the PBM) were used to prohibit the identification of the patient, pharmacy and physician; thus maintaining anonymity.

1.5.4 Classification systems used in the research project

Different classification systems were used during data analysis. These included classification systems to classify ARV medication and measures that were analysed.

1.5.4.1 Medication

Two classification systems were used during this study, which will be discussed subsequently: The NAPPI Code, and *Mims*™ Classification.

- **The NAPPI Code (National Pharmaceutical Product Interface –Codes for medication)**

Every active agent on the database has a NAPPI code as indicated by Snyman (2009:11a). This is a nine-digit code and a unique identifier for any given product implemented with electronic use in mind. The NAPPI code allows the dispenser to identify the brand, pack size, strength and manufacturer plus exclusion of the product dispensed (Health Web, 2008). The NAPPI codes for the ARVs were used to extract the data from the databases and to run the necessary queries in SAS 9.1® (SAS Institute Inc, 2006-2007).

- **The Mims™ (Monthly Index of Medical Specialties) Classification**

The *Mims*™ classification system classifies medicines according to their pharmacological actions (Snyman, 2009:11a). The Mims™ classification was used as the criterion to classify the ARVs and also to run queries in SAS 9.1® (SAS Institute Inc, 2006-2007).

1.5.4.2 Age groups

Young people in Sub-Saharan Africa continue to be one of the population groups at greatest risk for HIV infection, particularly young women (UNAIDS, 2004). According to Makubalo *et al.* (2004:8), based on the 2003 South African antenatal clinic survey, HIV prevalence among 15 to 19-year-old women appeared to be stabilising at around 15% whereas with the 20 to 24-year-old age group, the prevalence increased from 2002 levels to 30%. A report of the mid-year population estimates for SA 2008, revealed that nearly one-third

(32%) of the population was younger than 15 years and of these approximately 22% (3.4 million) live in KwaZulu-Natal and 19% (2.94 million) live in Gauteng (Statistics South Africa, 2008:3).

The Statistical Analysis System®, SAS 9.1® (SAS Institute Inc, 2006-2007) programme was used to calculate the age of a patient on the date of dispensing the prescription, thus calculated from the date of birth of the patient and the date of dispensing the prescription.

The PBM's data were divided into five different age groups, namely children, adolescents, young adults, older adults and the elderly. The division of the age groups into their various categories is illustrated in the Tables 1.5 and 1.6 below.

This age group was used to demonstrate DDIs between ARVs prescribed in different age groups in a study performed in SA by Katende-Kyenda *et al.* (2008c:397) using data that were obtained from the medicine claims database of a PBM Company. The age category used in the study is demonstrated in Table 1.5. The age of patients in database A was available for 2006 only, which could not be used in database B for 2005-2007.

Table 1.5: Categories of age groups used in database A

Age group	Years	Description
1	0≤6	Children ≤ 6 years of age
2	6≤12	Children 6 < and ≤ 12 years of age
3	12≤19	Young adults12 < and ≤ 19 years of age
4	19≤40	Adults 19 < and ≤ 40 years of age
5	40≤60	Adults 40 < and ≤ 60 years of age
6	>60	Adults > 60 years

Table 1.6: Categories of age groups used in database B

Age group	Years	Description
1	0≤12	Children ≤ 12 years of age
2	12≤19	Children 12 < and ≤ 19 years of age
3	19≤45	Young adults 19 < and ≤ 45 years of age
4	45≤59	Adults 45 < and ≤ 59 years of age
5	>59	Adults > 59 years of age

This age grouping was used to demonstrate the total number of ARV prescriptions and potential DDIs according to different age groups and different prescribers in a study by Katende-Kyenda *et al.* (2009b), performed in SA using data that were obtained from a medicines claims database of a PBM company. Furthermore the same age grouping was used to demonstrate the total number of ARV drug regimens prescribed by general practitioners (GPs) and specialists (SPs) with PDDs not according to the recommended ARV dosing and age group for three years in a study by Katende-Kyenda *et al.* (2009c).

1.5.4.3 Gender

SA is one of the countries in Sub-Saharan Africa hardest hit by the HIV epidemic. In a cross-sectional, national representative, household survey, women were found to be four times more likely to be infected with HIV in comparison with men of the same age (Pettifor *et al.*, 2005:1531). This gender inequality had been noted in a number of surveys throughout Sub-Saharan in Tanzania, Zimbabwe and Kenya (Obasi *et al.*, 2001:517; Gregson *et al.*, 2002:1896; Glynn *et al.*, 2001:S52).

The WHO (2007) defines sex as the biological and physiological characteristics that define the socially constructed roles, behaviours, activities, and attributes that society considers appropriate for men and women. In other words male and female are sex categories and masculine and feminine are gender categories (WHO, 2007). Sex refers to an individual's gender classification: male or female (Anon, 2007).

For the purpose of this research project gender and sex will be regarded as synonyms and will be used to indicate whether a prescription was prescribed for a male or female patient. Furthermore, only patients whose gender group (i.e. male or female) could be obtained from the available data were included. A third sex group was included namely all patients whose gender was unknown to the PBM. This can be the result of the medical scheme not supplying the sex of the patient to the PMB. The gender was only available for 2006 in the database A.

1.5.4.4 Prescriber type

Data from database B were also divided according to prescriber type (i.e. person writing the prescription). The prescribers were divided into the following categories:

- General medical practitioners: This group includes all the medical providers that are registered with the Health Professions Council of South Africa (HPCSA) as a general medical practitioner (GP).

- Prescribers from the following specialist areas (SP) which include the following prescribers: Anaesthesiology, cardiology, paediatrics, clinical haematology, dermatology, gastroenterology, neurology, obstetrics and gyneacology, oncology, ophthalmology, oral pathology, orthodontics, orthopaedics, otorhinolaryngology and clinical pharmacology.

1.5.5 Descriptive measures

Various descriptive measures, such as prevalence according to age and gender, PDD and prevalence of prescriptions with potential DDIs were used to achieve the specific objectives as stated in Section 1.4.2. These measurements will be discussed in the following subsections:

1.5.5.1 Prevalence

According to Waning and Montagne (2001:20) prevalence is the number of existing cases of an illness in a defined population at a specific time. In this research project, prevalence and frequency were used as synonyms and regarded as an indication of the number of medicine items/prescriptions or specific medicine items (according to trade name, active ingredient, or pharmacological group) claimed for a specific time period or for a specific group of patients (e.g. specific age group or gender). Prevalence was used in this study to describe the prevalence of prescriptions with potential DDIs between ARV agents according to age group and prescriber type on the PMB's database.

1.5.5.2 Potential DDIs

Although DDIs is a major challenge to the health care systems, representing a significant opportunity cost for health care, it is widely under-recognised source of medication errors (Seden *et al.*, 2009:5). Prescriptions with potential DDIs lead to adverse clinical outcomes such as hospital admissions and emergency department visits (Yee *et al.*, 2005:1652), and they have been found to account for 5.2% of 209 hospital admissions in patients receiving ARV drugs in Baltimore (Rastegar *et al.*, 2006:933).

In this research project potential DDIs between different medicine items were identified and classified according to a clinical significant rating. The formula for the clinical significance rating of potential DDIs are described in the form of three degrees of severity, identified as major, moderate and minor as described by Tatro (2008). Drug interactions assigned documentation levels of established, probable, or suspected are considered to be well-substantiated and have clinical significance ratings of 1, 2 or 3. These interactions have

a probability of occurring, while interactions of clinical significance ratings 4 and 5 are not substantiated – having documentation levels of possible or unlikely (refer to Table 1.7) (Tatro, 2008).

Table 1.7: Tatro classification of DDIs

Clinical Significance rating	Severity	Documentation
1	Major	Suspected or greater
2	Moderate	Suspected or greater
3	Minor	Suspected or greater
4	Major/Moderate	Possible
5	Minor/any	Possible or unlikely

1.5.5.3 Prescribed Daily Doses (PDDs)

According to WHO (2003:38), the PDD is defined as "*the average dose prescribed according to a representative sample of prescriptions.*" It is of great importance that the PDD be related to the diagnoses made for the prescribed medication. The average daily amount of a drug prescribed can be determined through the PDD. The PDD is important in those drugs where the dosage differs from one indication to another.

PDD of a drug can be calculated by multiplying the number of tablets (or amount of suspension or syrup) dispensed during the treatment period and the strength per tablet (or per ml), divided by the days supplied (NHS, 2009).

1.5.6 Data analysis

The Statistical Analysis System®, SAS 9.1® (SAS Institute Inc., 2006-2007) was used to analyse the data in consultation with the Statistical Consultation Service at the North-West University (NWU). Various descriptive statistics such as the frequency, arithmetic mean (average), and standard deviation and effect sizes were used to describe the characteristics of the study population within individual studies within the project. These statistics were discussed in the different articles.

1.5.7 Reliability and validity of the research instruments

The data were obtained directly from the two medicine claims databases A and B of the two PBM companies and the researcher could not change the data. The research was conducted with the assumption that all data obtained from the databases were correct and accurate.

1.5.8 Ethical aspects

Permission to conduct the study was granted by the two PBM companies. Ethical approval was obtained from the North-West University's ethical committee with the ethical number: North-West University 07M01, and Walter Sisulu University (WSU), Mthatha campus, Research Committees.

1.5.9 Report and discussion of the results of the empirical investigation

The research articles are included in Chapter 3.

1.5.10 Selection of research articles

The study consisted of six research articles that were published or have been submitted for publication in peer-reviewed (refereed) scientific journals. The findings evaluated the prevalence of DDIs between ARV agents in a section of a private health care sector in SA. The articles have been published or have been accepted for publication or have been submitted for publication in peer-reviewed journals, thus fulfilled the general research objective of the study. The titles of the articles plus the databases where data were obtained are shown in Table 1.8 and are listed below:

- Prevalence of drug-drug interactions of antiretroviral agents in the private health care sector in South Africa. 2008. *South African Medical Journal*, 98(2):109-113. This is an accredited journal.
- Effect of Prescribed Minimum Benefits on the prevalence of drug-drug interactions of antiretroviral agents in a section of the private health care sector in South Africa: A two-year comparative study. 2008. *International journal of pharmacy practice,* 16:403-408. Was on the list of accredited journals in 2007 when the manuscript was accepted for publication.
- Prevalence of possible drug-drug interactions between antiretroviral agents in different age groups in a section of the private health care sector setting in South Africa. 2008. *Journal of clinical pharmacy and therapeutics,* 33: 93-400. This is an accredited journal.

- Analysis of possible drug-drug interactions between ritonavir and other antiretroviral drugs in a private health care sector in South Africa. 2009. *African journal of primary health care and family medicine*, 1(1): 1-6.
- The identification of potential drug-drug interactions between antiretroviral drugs and the usage of Prescribed Daily Doses in the evaluation of these interactions in a section of the private health care sector in South Africa. (Accepted for publication in: *International journal of STD & AIDS*: Date accepted 17th August 2009). This is an accredited journal.
- Longitudinal analysis of the prevalence of antiretroviral potential drug-drug interactions on prescriptions of general practitioners and specialists in South Africa and the evaluation of the prescribed daily doses of the interacting drugs. (Submitted to *Pharmacoepidemiology and drug safety* on the 16th Oct. 2009). This is an accredited journal.

1.5.11 Limitations to the study

The limitations to the study are discussed in Chapter four where the results are discussed, and conclusions and recommendations made.

1.5.12 Conclusions and recommendations based on the results of the empirical investigation

Conclusions based on the results of the study are offered in Chapter four, as well as recommendations made in relation to the findings derived from the results.

Table 1.8: Different databases used to achieve the different research objectives in the different articles

Article	Database	Year	Number of ARV prescriptions	Number of patients	Number of patients on ARV treatment
Prevalence of drug-drug interactions of antiretroviral agents in the private health care sector in South Africa. 2008. *South African Medical Journal*, 98(2):109-113	A	2004	43 482	657 009	9065
Effect of Prescribed Minimum Benefits on the prevalence of drug-drug interactions of antiretroviral agents in a section of the private health care sector in South Africa: A two-year comparative study. 2008. *International journal of pharmacy practice*, 16:403-408.	A	2004 2005	43 482 51 613	657 009 379 352	9065 9290
Prevalence of possible drug-drug interactions between antiretroviral agents in different age groups in a section of the private health care sector setting in South Africa. 2008. *Journal of clinical pharmacy and therapeutics*, 33:93-400.	A	2006	47 085	275 424	8 999
Analysis of possible drug-drug interactions between ritonavir and other antiretroviral drugs in a private health care sector in South Africa. 2009. *African journal of primary health care and family medicine*, 1(1): 1-6.	A	2004 2005 2006	43 482 51 613 47 085	657 009 379 352 275 424	9065 9290 8 999
The identification of potential drug-drug interactions between antiretroviral drugs and the usage of Prescribed Daily Doses in the evaluation of these interactions in a section of the private health care sector in South Africa. (Accepted for publication in: *International journal of STD & AIDS*: Date accepted 17th August 2009)	B	2005 2006	49 995 81 096	1 218 358 1 259 099	7 664 10 162
Longitudinal analysis of the prevalence of antiretroviral potential drug-drug interactions on prescriptions of general practitioners and specialists in South Africa and the evaluation of the prescribed daily doses of the interacting drugs. (Submitted on 16th Oct. 2009) to *Pharmacoepidemiology and drug safety*).	B	2005 2006 2007	49 995 81 096 88 988	1 218 358 1 259 099 911 212	7 664 10 162 10 061

1.6 DEFINITIONS

Certain terms used in this study may be interpreted differently by different people. It is therefore important to clarify the meanings of these terms within the context of this study and for this purpose the following definitions will be used:

Antiretroviral (ARV) drugs / ARV medicine items / ARV medication / ARVs:

All medication listed in the South African Medicines Formulary (SAMF) (Gibbon, 2008:318) as "Chemotherapy of HIV", thus all antiretroviral agents used to prevent infection (following exposure or to prevent mother-to-child transmission) or to treat established HIV infection. Antiretroviral drugs are also referred to in this study as ARVs or ARV medicine items or ARV medication.

ART (antiretroviral therapy / treatment):

ART is the process of treating HIV/AIDs using a set of antiretroviral drugs in different combinations.

Drugs:

In the South African context the term "drug" might be interpreted as referring to drugs of abuse or otherwise to any chemical compound that may be used on or administered to humans or animals as an aid in the diagnosis, treatment or prevention of diseases or other abnormal condition or to control or improve any physiologic or pathologic condition. For the purpose of this study the term "drug" is used in terms of the latter explanation and refers not only to the pharmacological active ingredient, but also to the total pharmaceutical product or medicine.

Drug-drug interaction:

The term drug-drug interactions can be defined as "*the pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone*" (Tatro, 2005).

Medicine / medicine item:

In the South African context a medicine refers to *"any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine;"* (Medicines and Related Substances Control Act (101/1965). In the SA context a prescription can consist of one or more medicine items.

Prescriber:

According to the Medicines and Related Substances Control Act (101/1965) 'authorised prescriber' means "*a medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974*".

Prescription:

A prescription is a legal document written by an authorised prescriber for a specific patient and contains one or more medicine items and directions to use these medications.

1.7 OUTLINE OF THE STUDY AND CHAPTER SUMMARY

In Chapter 1, the background to the study, the problem definition, the aim and objectives of the study, as well as the research methodology were outlined. Specific attention has been paid to private and public health care. Aspects of access and delivery of private vs public health care, as related to the delivery of HIV/AIDS treatments within the framework of PMBs were addressed.

This chapter also provided an overview of the methodologies used to generate results for the individual articles published (or in review). However, due to the nature and extent of this study, literature regarding HIV/AIDS in SA and worldwide in terms treatment protocols, DDIs in terms of concept, different types, mechanisms, dynamics and rating system received further attention in Chapter 2. Furthermore the following aspects were reviewed: causes, general incidence, frequency of DDIs, clinically significant DDIs, risk factors for DDIs in ARVs, the pharmacological aspects of DDIs in ARVs and management of DDIs in ARVs, the role of the pharmacist in detecting DDIs. Finally ways of detecting, preventing and managing DDIs in clinical practice were discussed.

Chapter 3 will contain copies of articles that have been published. In Chapter four the general findings of the study are discussed according to the objectives of the study. Thereafter, conclusions, recommendations and limitations of the study are outlined in the same chapter.

CHAPTER 2

RECOMMENDED MANAGEMENT GUIDELINES AND DDIs FOR HIV/AIDS

The recommended management guidelines for HIV/AIDS will be discussed in this chapter with specific reference to the South African guidelines and they will be compared to management guidelines of other countries worldwide. Thereafter a discussion on DDIs as a complication of HIV/AIDS management, in terms of concept, types, mechanisms, dynamics and system ratings will follow. The prevalence and risk factors for DDIs in clinical practice will follow, and then the pharmacological aspects of DDIs of ARVs. Finally the focus will be on management, control and the role of pharmacists in preventing DDIs in clinical practice..

2. 1 INTRODUCTION

HIV/AIDS is a chronic lifelong disease with no known cure; therefore, patients living with HIV infection require medical care for life (Sterne, 2005:378). The core component of treatment and care for the patient is the provision of antiretroviral treatment (ART). Optimal ART increases the length and quality of life of HIV-infected patients, thus changing the natural history of HIV infection, and reducing its onward transmission (Yeni *et al.,* 2002:222). According to Gilks (2006:505), the WHO promotes a public health approach to ART. This promotes the rational selection of different drug classes into first and second regimens; simplified and standardised clinical management; standardised record keeping; minimisation of drug toxicity and side effects; maximising adherence; the supports of the clinical, virological and epidemiological goals of ART (Bartett & Gallant, 2003).

According to the WHO (2009b:1), more than 6 800 people worldwide become infected with HIV every day with more than 5 700 dying, due to inaccessibility to HIV prevention, treatment and care services. The HIV pandemic remains the most serious infectious disease challenge to global public health (WHO/UNAIDS, 2007). During December 2007, an estimated 3 million people living with HIV were receiving ART in low- and middle-income countries, representing 31% of the estimated 9 million people in need of treatment (WHO, 2008a:15). It was reported in a progress report for universal access to ART that the greatest increase in the number of HIV patients receiving treatment was in Sub-Saharan Africa, with access to ART among women being higher than among men (WHO, 2008a:15). According to the UNAIDS report (2008), the actual data for the number of people in need of ART in SA were not available. However, it was estimated that 5.7

million people had already been infected and some would need treatment. Despite the initial slow progress of the ARV roll-out, a report from the JOURNAIDS (2008), stated that there had been 411 889 people on ARVs by 2008. About 97% of adults and children on therapy in low- and middle-income countries are receiving first-line ARV drug regimen treatment, though the average price of second-line regimens remains high in low- and middle-income countries (WHO, 2008a:15).

However, the number of HIV infections remain high with an estimation of 2.5 million deaths in 2007, due to many people not being able to access HIV prevention services due to unavailable or limited resources as Langa (2009) stated "*I have seen other people die and it scares me.*" This was further confirmed by Chigwedere *et al.* (2008:410) in a study seminar that 330 000 lives had been lost in SA between 2000 and 2005 due to a non-implementation of the ART programme. This was due to the South African Government policies restricting or delaying the use of ARVs. A report from WHO (2005a:1) on the regional for South–East Asia, stated that, it is estimated that if not treated, 3 million people, would die every year of HIV/AIDS, and most of these would be in 34 high burden countries of Africa and Asia (WHO, 2005a:1). The current commitment should be to "universal access" establishing an environment in which HIV prevention, treatment, care and support interventions are available, accessible and affordable to all who need them, covering a wide range of interventions that are aimed at individuals, households, communities and countries (Global HIV Prevention Working Group, 2004:1).

There is a need for scaling up a comphrensive package of HIV prevention, treatment, care and for strengthening health care systems through the mobilisation of partners from many sectors. According to the WHO progress report in February 2009, priorities were established under four strategies for action to be taken to make significant progress towards achieving the universal access goal. These were to (WHO, 2009b:2):

- Enable people to know their HIV status.
- Maximise the health sector's contribution to HIV prevention.
- Accelerate the scale-up of HIV/AIDS treatment and care, strengthening and expanding health systems.
- Investigate strategic information to guide a more effective response.

According to the WHO (2009b:7), HIV/AIDS department, a comprehensive response to HIV/AIDS is achieved if the health sector takes responsibility for delivering interventions to prevent new HIV infections, and to improve quality of life and avert premature death in adults and children living with HIV/AIDS. The priority interventions that are recommended by the WHO include providing knowledge of HIV status, preventing transmission of HIV and other sexually transmitted infections and providing treatment and care for HIV/AIDS.

2.2 DIFFERENT MANAGEMENT STRATEGIES FOR HIV/AIDS

In this section, the different management strategies employed to manage HIV/AIDS will be discussed with specific reference to the recommended treatment guidelines using ARV agents.

2.2.1 WHO recommendations for management of HIV/AIDS

The proper management of patients living with HIV is a comprehensive lifelong process focusing on the patient's needs, and according to the WHO Department of HIV/AIDS this process involves (WHO, 2009b:6):

- Initial HIV testing and confirmation of the results.
- Appropriate counselling during the process of identifying HIV infection.
- Clinical evaluation.
- Patient counselling.
- Monitoring patient health.
- Initiating ART and its maintenance.
- Prevention and treatment of opportunistic infections (OIs), other coinfections and co-morbidities.
- Psychological support.
- Adherence support.
- Referrals to provide community care.

2.2.2 Prevention of HIV in infants and young children

According to WHO recommendations, a comprehensive approach to preventing HIV in infants and children consists of four elements namely (WHO, 2009b:26):

- Primary prevention of HIV transmission.
- Prevention of unintended pregnancies among women living with HIV.
- Prevention of HIV transmission from women living with HIV to their children.
- Provision of treatment, care and support to women living with HIV, their children and families.

2.2.3 WHO recommended ART to prevent HIV infection in infants

As HIV can be transmitted from mother to infant during pregnancy, delivery or through breastfeeding, interventions are necessary to avoid the transmission. It has been reported that an estimated 20% to 25% of infants of HIV-infected mothers will acquire HIV up to and including delivery (WHO, 2009b:28). Therefore it is necessary to reduce the HIV transmission to the infant by the use of ARV drugs and avoiding breastfeeding, thus promoting child survival. Therefore WHO recommends that (WHO, 2009b:28)

- all pregnant women with HIV should receive ARV medicines, either ART for life or combined ARVs for prophylaxis, to reduce vertical transmission;
- women with clinical and/or immunological criteria should start ART and do so as early as possible in pregnancy;
- pregnant women with HIV who are at clinical stage 3 (refer to Section 2.3.2.1.1) with CD4 < 340 cells/mm^3 should start ART;
- pregnant women with HIV who need ART be treated with a full combination regimen, with azidothymidine (AZT)-containing regimens;
- HIV-positive women who are not in need of ARVs, should receive combination ARV regimen for prophylaxis;
- the HIV-exposed infant requires ARV prophylaxis at birth; and
- HIV-positive women, who present to health services late in pregnancy or at labour and delivery, should also receive ART as well as the newborn.

The recommended first-line combination ART for pregnant women is shown in Table 2.1 (WHO, 2009b:29).

Table 2.1: Recommended first-line combination ARV regimens for a pregnant women

Mother	Treatment
Antepartum	AZT and 3TC and NVP – twice daily
Intrapartum	AZT and 3TC and NVP – twice daily
Postpartum	AZT and 3TC and NVP – twice daily

AZT: azidothymidine, 3TC: lamivudine, NVP: nevirapine

Table 2.2 (WHO, 2009b:29) shows the recommended ARV regimen for prophylaxis in pregnant women not eligible for ART and the recommended ARV regimens for prevention of resistance and prophylaxis of intra-partum transmission in infants can be seen Table 2.3 (WHO, 2009b:29).

Table 2.2: Recommended ARV regimens for prophylaxis in pregnant women not yet eligible for ART

Mother	Treatment
Antepartum	AZT starting at 28 weeks of pregnancy or as soon as feasible
Intrapartum	Single dose (Sd)-NVP and AZT/3TC
Postpartum	AZT/3TC for 7 days

AZT: azidothymidine; 3TC: lamivudine, NVP: nevirapine.

Table 2.3: Recommended ARV regimens for prevention of resistance and prophylaxis of intra-partum transmission in infants

Infant	Treatment
At least 4 weeks maternal ART	AZT for 7 days
Less than 4 weeks maternal prophylaxis ART	AZT for 4 weeks
At least 4 weeks maternal prophylaxis ARV	Sd-NVP and AZT for 7 days
Less than 4 weeks maternal prophylaxis ARV	Sd-NVP and AZT for 4 weeks

ART: Antiretroviral therapy, ARV: Antiretroviral, AZT: azidothymidine, NVP: nevirapine.

2.2.4 Recommended ART to prevent HIV infection in infants in other countries

In the **United States of America**, interventions for prevention of perinatal HIV-1 transmission were put in place about a decade ago (Public Health Service Task Force, 2008:1). Most HIV-1-infected pregnant women received care for HIV infection during the prenatal period. The same approach as recommended by the WHO (refer to Section 2.2.3; Tables 2.1-2.3) was followed, they receive the combination ART with three or more drugs and had access to obstetric interventions such as scheduled caesarean sections at 38 weeks' gestation and avoiding breastfeeding (Cooper *et al.*, 2002:484).

In **SA** the prevention of mother-to-child-transmission (PMTCT) according to the National Department of Health should consist of the following (National Department of Health, 2005:10):

- Optimal antenatal care that includes good nutrition, iron and multivitamin syrup.
- Addressing all issues with an increased risk of premature labour.
- Prevention and management of infections like sexually transmitted diseases (STIs), urinary tract infections (UTIs), malaria and pneumocystis jiroveci (PJP).

- Administering a single dose of nevirapine given at the onset of labour and to the neonate as soon as possible after birth. Pregnant women meeting the criteria for initiation of ART should receive triple therapy. Non-breastfeeding women receive a combination of AZT and NVP.
- Avoiding nevirapine for pregnant women who qualify for ongoing ART since it is associated with a higher risk of hepatitis and women with a CD4 count > 250 cells/mm^3 (Regensberg & Makiwane, 2009:70).
- Starting ART for women who do not need long-term therapy in the second trimester and AZT, lamivudine (3TC) and lopinavir/ritonavir or nelfinavir is recommended (Regensberg & Makiwane, 2009:71). The neonatal AZT dose is shown in Table 2.4 (Regensberg & Makiwane, 2009:71.

Table 2.4: Neonatal AZT dose

AZT oral
Term 4 mg/kg 12 hourly
• 30 – 34 weeks 2 mg/kg twice daily for 2 weeks, then 2 mg/kg three 8 hourly for 2 weeks
• < 30 weeks 2 mg/kg 12 hourly for 4 weeks
AZT IVI (if infant per mouth)
• Preterm 1.5 mg/kg 12 hourly
• Term 1.5 mg/kg 6 hourly.

AZT: azidothymidine, IVI: Intravenous infusion.

According to the National ART and care guidelines for adults and children in **Uganda** as quoted by Katabira and Kamya, Ministry of Health (2003:41), the recommended regimens for preventing mother to child transmission (PMTCT) are shown in Table 2.5.

Table 2.5: Recommended regimens for PMTCT intervention in Uganda

Target	Nevirapine (NVP)	Zidovudine (AZT)
Mother	200 mg stat at the beginning of labour or latest 30 minutes before delivery	• 300 mg twice daily for at least 4 weeks before delivery **then** • 300 mg every 3 hours during labour **then** • 300 mg twice daily for one week after delivery
Infant (within 72 hours of birth)	Syrup 2 mg/kg stat	Syrup 5mg/kg twice daily for one week

The Federal Ministry of Health in **Ethiopia**, as quoted by Tekle adopted the WHO/UNICEF/UNAIDS 4-prolonged PMTCT strategy as a key entry point to HIV care for pregnant women. The four prongs are (The Federal Ministry of Health (2007:3) :

- Primary prevention of HIV infection.
- Prevention of unintended pregnancies among HIV-infected women.
- Prevention of HIV transmission from infected women to their infants.
- Treatment, care and support of HIV-infected women, their infants and their families.

In the **United States**, according to the Public Health Service Task force (PHSTF), ARV prophylaxis is recommended for all pregnant women with HIV infection, regardless of the viral load (PHSTF, 2008:15). The task force employed the WHO recommended guidelines of the combination ARV regimens containing three drugs for the prevention of perinatal HIV transmission. The regimen should consist of zidovudine, lamivudine and abacavir.

2.3 TREATMENT AND CARE INTERVENTIONS

The management of the full range of HIV-related conditions should be based on clear guidelines and standardised protocols that include (WHO, 2009b:39)

- regular periodic clinical assessment, both pre-ART and post-ART;
- treatment preparedness and adherence support;
- management of opportunistic infections and co-morbidities;
- prevention and treatment of mental health disorders; and provision of palliative care.

2.3.1 ART for adults, and children

In the management of HIV infection with ART, the main goals should be (Bartlett & Gallant, 2003)

- clinical prolongation and improvement of the quality of life;
- quantitative and qualitative immunological reconstitution of the infected person so as to prevent the onset of opportunistic infections;
- maximising possible reduction of the viral load for the longest possible time to curb the progression of the disease, thus preventing the development of drug resistance; and
- reducing the prevention of onward HIV transmission.

2.3.2 Treatment and care intervention for HIV-infected people

According to the WHO (2009b:39), the management of the full range of HIV-related conditions should be based on clear guidelines and standardised protocols set out by each country. Treatment and care interventions should include the following (WHO, 2009b:39):

- Both pre-ART and post-ART periodic regular clinical assessment.
- Treatment preparedness and adherence support.
- Management of opportunistic infections and co-morbidities.
- Prevention and treatment of mental disorders.
- Palliative care.

2.3.2.1 ART for adults and children

The public health sector approach to ART is to facilitate the quality of HIV treatment for all who need it (National Department of Health, 2004:2). The universal access goal is to promote simplified and stardardised clinical decision making, drug regimens and patient data recording systems. According to the WHO (2009b:40), this goal is only achieved if different countries develop national strategies for HIV drug resistance prevention coupled with assessment so as to maintain the effectiveness of first- and second-line ARV regimens. Furthermore it is the recommendation of the WHO (2009b:41) that laboratory services for the diagnosis and treatment of HIV be expanded and improved, as well as the effective treatment.

The public health care sector approach to scaling up ART, according to Gilks *et al.* (2006:505) stated the principles of simplification, standardisation, decentralisation, equity and participation of people receiving

ART and the community. The main components of the approach were stated to be the following (Gilks *et al.*, 2006:506):

- Standardising regimens and simplifying formularies.
- Simplifying clinical decision making and standardising treatment monitoring.
- Standardising management of toxicity and DDIs.
- Monitoring HIV drug resistance at the population level.

Cohort studies performed by Salzberger *et al.* (2004:491) and Palella *et al.* (2003:620) showed that the best primary markers for initiation of ART are clinical staging (stage 3 or 4) (refer to Section 2.3.2.1.1) and CD4 counts with the viral load being the secondary marker. It is also recommended that prior to starting ART, support to ensure adherence is initiated. Recommendations for initiating ART in adults and children are shown in the Tables 2.6, 2.7 and 2.8 (WHO, 2009b:40-42).

Table 2.6: WHO recommendations for initiating ART in adults

WHO clinical stage	CD4 testing	
	Not available	**Available**
1	Do not start ART	Start ART if CD4 is < 200 cells/mm^3
2	Do not start ART	
3	Start ART	Consider starting ART if CD4 < 350 cells/mm^3, starting before it drops to < 200 cells/mm^3. Recommended for all HIV+ pregnant women if CD4 < 350 cells/mm^3
4	Start ART	Start all irrespective of CD4

2.3.2.1.1 WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

The WHO clinical staging of HIV/AIDS is valuable in terms of prognosis and the initiation of therapy and it consists of four clinical stages as shown in Table 2.6 and as outlined below (Regensberg & Makiwane, 2009:8; National Department of Health, 2004:78):

Clinical Stage 1:

Clinical stage 1 consists of the following symptoms:

- Asymptomatic.
- Persistent generalised lymphadenopathy.

- Acute retroviral infection (sero-conversion illness) and/or performance scale 1: asymptomatic, normal activity.

Clinical Stage 2:

Clinical stage 2 consists of the following symptoms:

- Unexplained weight loss (<10% of presumed or measured body weight).
- Minor mucocutaneous (e.g. seborrhoea, prurigo, fungal nail infections, oral ulcers, angular cheilitis).
- Herpes zoster within the last five years.
- Recurrent upper respiratory tract infections (URTI) (e.g. bacterial sinusitis), and/or performance scale. 2: symptomatic, normal activity.

Clinical Stage 3

In clinical Stage 3 the following symptoms will be observed:

- Unintentional weight loss >10% of body weight.
- Chronic diarrhoea for longer than one month.
- Prolonged fever > one month.
- Oral candidiasis.
- Oral hairy leukoplakia.
- Pulmonary TB within the last year.
- Unexplained anaemia (< 8 g/dl), neutropaenia (< 0.5 x 109 per litre) and/or chronic thrombocytopaenia (< 50 x 109 per litre).

Clinical Stage 4 (AIDS)

Clinical stage 4 will be characterised by the following:

- HIV-wasting syndrome.
- Pneumocystis pneumonia.
- Recurrent severe bacterial pneumonia.
- Chronic herpes simplex infection.
- Oesophageal candidiasis.
- Disseminated myocosis.
- Recurrent septicaemia.
- Invasive cervical carcinoma.
- Atypical disseminated leishmaniasis.
- Symptomatic HIV-associated nephropathy.
- Symptomatic HIV-associated cardiomyopathy.

Table 2.7: WHO recommendations for initiating ART in infants and children

Criteria to start ART in infants and children				
Age	**Infants younger than 12 months**	**12 months to 35 months**	**36 months to 59 months**	**5 years or older**
% CD4	All	< 20	< 20	< 15
#Absolute CD4		< 750	< 350 cells/mm^3	(< 200 cells/mm^3)

 # Absolute CD4 count is naturally less constant and more age-dependent than %CD4; it is not therefore appropriate to define a single threshold.

There are possibilities of DDIs between the above recommended regimens (refer to Tables 2.1 – 2.4). It has been reported that there are a few pharmacodynamic interactions between zidovudine (NRTI) and stavudine (NRTI) if co-administered (Piscitelli & Gallicano, 2001:984). There are also possible DDIs in NNRTIs like efavirenz and nevirapine, since they are extensively metabolised via CYP3A4 and can either act as inducers or inhibitors of CYP3A4 (Piscitelli & Gallicano, 2001:985). All PIs (ritonavir, saquinavir, indinavir) are potent inhibitors of CYP3A4, and therefore they are prone to DDIs (Fichtenbaum *et al.*, 2002:569).

Table 2.8: Summary of WHO preferred ART recommendations for infants, children and adults

Patient group	Preferred first-line regimen	Preferred second-line regimen
Infants		
Infant not exposed to ARV	NVP and 2 NRTI	Boosted PI and 2 NRTI
Infant with unknown ARV exposure	NVP and 2 NRTI	Boosted PI and 2 NRTI
Infant exposed to NVP	LPV/RTV and 2 NRTI	NNRTI and 2 NRTI
Children		
Children 3 years or over	NNRTI and 2 NRTI	Boosted PI and 2 NRTI
Adult or adolescent		
Adult or adolescent	NNRTI and 2 NRTI	Boosted PI and 2 NRTI
Woman starting ART in pregnancy	NVP and AZT and 3TC	Does not apply
Woman starting ART within 6 months of single dose of NVP	NNRTI and 2 NRTI or 3 NRTI	Does not apply
Concomitant conditions		
Child, adolescent or adult with severe anaemia	NVP and 2 NRTI (avoid AZT)	Boosted PI and 2 NRTI
Child, adolescent or adult with TB	EFV and 2 NRTI or 3 NRTI	Boosted PI* and 2 NRTI
Adult or adolescent with Hepatitis B	TDF and 3TC and NNRTI	Boosted PI and 2 NRTI**
Adult or adolescent with Hepatitis C	EFV and 2 NRTI	Boosted PI and 2 NRTI
IDU	NNRTI and 2 NRTI	Boosted PI and 2 NRTI
HIV-2 or dual infection	3 NRTI	Boosted PI and 2 NRTI

* *If using RMP in the TB regimen, LPV/RTV and extra dose of RTV is the recommended PI option, based on pK interactions. If RFB or an alternative TB regimen without RMP is used, any bPI at its conventional dosage can be used.*

** *If long-term anti-HBV therapy is still needed, consider maintaining 3TC and/or TDF, in addition to the new 2NRTI backbone.*

NNRTI = Non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; IDU = injecting drug use; EFV = efavirenz; LPV/RTV = lopinavir /RTV = booster dose ritonavir, TDF = tenofovir, 3TC = lamivudine, RMP = rifampicin, RFB = rifabutin, HBV = Hepatitis B virus.

2.3.2.3 Managing opportunistic infections and co-morbidities

Opportunistic infections are the burden of HIV/AIDS and the prevalent co-morbidities, therefore standardised protocols should aim to manage the common acute and chronic conditions associated with HIV/AIDS. These

include infections such as Candida (oesophageal and mucosa), cryptococcal meningitis, cytomegalovirus, herpes zoster, pneumocystis pneumonia (PCP). A study performed by MacPherson *et al.* (2009:590) reported that TB as one of the opportunistic infections was the leading cause of death in HAART-treated adults accounting for 44.3% (47/106) of all deaths and diarrhoeal diseases accounted for 24.5%. Other prevalent conditions that need to be managed clinically are neurological, skin disorders, malignancies, cardiovascular and metabolic conditions and mental health (WHO, 2009b:43).

2.3.2.3.1 Managing TB

In many parts of the world, particularly in developing countries, HIV/AIDS epidemiology may overlap with other infections such as TB (Seden *et al.*, 2009:6). TB is the leading cause of HIV-related morbidity and mortality, accounting for about 12% of all HIV-related deaths (WHO, 2009b:49). This was confirmed by Lawn *et al.* (2006:1605), that although the incidence of TB is reduced dramatically by HAART, it remains the leading cause of morbidity and mortality, both in TB-treated and in HAART-treated adults. In countries with high HIV prevalence, up to 80% of the people with TB test positive for HIV infection, and those are likely to have reactivation and reinfection of TB (WHO, 2009b:49). Mukada *et al.* (2001:143) reported that in SA about 80% of patients presenting with active TB in the province of KwaZulu-Natal, were co-infected with HIV. WHO (2009b:49) recommends that TB and HIV/AIDS programmes collaborate and ensure the surveillance of HIV prevalence among TB patients. Co-trimoxazole and isoniazid preventive therapy should be used in such cases (WHO, 2009b:49).

The most effective approach to manage TB in people living with HIV is to investigate the patients for TB before starting ART (WHO, 2009b:49). If the patient develops TB while on ART, continue ART throughout TB treatment with changes in the regimens 1 and 2. To these on regimen 1 a change to efavirenz is recommended and to those on regimen 2, a change to lopinavir/ritonavir 400 mg/400 mg every 12 hours. If the patient presents with TB before commencing ART, with no history of WHO Stage 4 illness and a CD4 > 200 cells/mm.^{3} there is no need for ART. If the patient has a history of WHO stage 4 illness, and /or with a CD4 count < 200 cells/mm^3 complete 2 months of TB treatment before starting ART (National Department of Health, 2004:18; Regensberg & Makiwane, 2009:42).

2.3.2.3.1.1 Complications presenting with management of TB

TB therapy, like HIV treatment, is complicated by drug resistance and thus requires multiple agents, which present varying potential problems of interacting with ARVs (Seden *et al.*, 2009:6). Rifampicin, a first-line drug for TB, for example has significant drug interactions with the PIs and NNRTIs. It is therefore preferable

to use a regimen that does not interact significantly with rifampicin (Regensberg & Makiwane, 2009:42). The drugs with which rifampicin interacts are efavirenz, nevirapine, lopinavir/ritonavir and ritonavir. It has been reported that when rifampicin is co-administered with efavirenz, there are wide inter-individual variations in plasma efavirenz concentrations; therefore dose adjustments may be required in some patients (Friedland *et al.*, 2006:1299). Furthermore, potential drug interactions exist between other rifamycins like rifapentine, and rifabutin because they are inducers of CYP3A4, and therefore reduce plasma concentration of PIs and NNRTIs. Delavirdine and PIs inhibit CYP3A4, thus increasing plasma concentrations of rifabutin (Burman & Jones, 2001:7).

2.3.3 South African National ART Guidelines

In SA the HIV/AIDS strategic plan for 2007-2011, as unveiled by the then deputy president in 2007, Mrs. Mlambo-Ngcuka, at the National Consultative Conference on March 2007, flows from the National Strategic Plan of 2000 to 2005 as well as the operational plan for comprehensive HIV/AIDS care, management and treatment (South Africa, 2007:8). HIV and AIDS can be considered one of the main challenges facing the country. In 2006 it was estimated that 39.5 million people worldwide were living with HIV, of those more than 63% were from Sub-Saharan Africa (UNAIDS, 2007:1). In 2006, about 5.54 million people were living with HIV infection in SA with 18.8% of the adult population (15 to 49 years), and 294 000 children aged 0 to 14 years (Dorrington *et al.*, 2006:8).

The challenge of HIV/AIDS in SA required an intensified comprehensive, multi-sectoral national response that had to address the social and economic realities that make certain segments of society more vulnerable, provide tools for prevention and provide designated providers to mitigate the wide-ranging impacts of the epidemic (South Africa, 2007:22).

The private health care sector in SA recognised the importance of providing comprehensive care to people living with HIV infection. Therefore in May 1998, Aid for AIDS (AfA) Clinical Guidelines was launched (refer to Section 1.2.7) to manage the outpatient benefits which a few contracted medical schemes had made available to cover the costs of ART, chemoprophylaxis and treatment of certain HIV-associated conditions (Regensberg & Makiwane, 2009:6).

The AfA programme was used to demonstrate the typical scope of HIV/AIDS disease management with the following objectives (McLeod *et al.*, 2003:84):

- To provide managed access to ART.
- To facilitate access to benefits for the treatment of post-exposure prophylaxis.

- To provide therapy for the prevention of MTCT.
- To offer expert advice to the primary care physicians of the member's choice.
- To provide a comprehensive education and awareness programme to members and employee groups.
- To assist with medications related to problem and lifestyle issues by means of nurse counsellors.

The disease management programmes were introduced in order to provide a comprehensive management approach for beneficiaries of contracted medical schemes. The members were required to register for the programmes in order to receive more generous benefits. In case of HIV/AIDS, systems have been created within these programmes to ensure client confidentiality. Disease management programmes can potentially improve cost-effectiveness. Specific case management and treatment protocols have been found by AfA to significantly reduce hospitalisation, outpatient and other medication costs (McLeod *et al.*, 2003:85).

PMB are described in Section 29(1) (o) and Regulation 7 of the Medical Schemes Act (131/1998). According to the act, all medical schemes in SA must offer a minimum level of benefits to employees with HIV/AIDS, called Prescribed Minimum Benefits (PMBs) for HIV/AIDS. The medical schemes must pay for the following (Council for Medical schemes, 2009c:8; Da Silva & Wayburne, 2008:41):

- Voluntary counselling and testing.
- Co-trimoxazole as preventative care.
- Screening and preventative therapy for TB.
- Diagnosis and treatment of sexually transmitted infections.
- Treatment of common opportunistic infections as a result of HIV/AIDS.
- Mother to child transmission (MTCT) prevention.
- Post exposure prophylaxis (PEP) – diagnosis and treatment.
- Pain management and palliative care.
- Medical management and medication, including the provision of ART.
- Ongoing monitoring for medicine effectiveness and safety.

2.3.3.1 HIV/AIDS management in the private health care sector of SA

According to the HIV/AIDS benefit management report, the benefits provided and managed by the 77 medical schemes in 2002 were analysed and divided into four categories (McLeod *et al.*, 2003: 83):

- Medical schemes that provide no HIV benefits other than PMBs.
- Medical schemes that provide additional HIV benefits but are not managed by any disease management programme.

- Medical schemes that provide additional HIV benefits and are managed by AfA, a programme regarded as the industry benchmark.
- Medical schemes that provide additional HIV benefits and are managed by another disease management programme, including their own in-house programme.

2.3.3.2 Treatment and preventive therapy for HIV-related conditions

The PMBs for HIV/AIDS place emphasis on counselling, testing for HIV and the treatment of people with HIV for opportunistic infections such PCP and tuberculosis (McLeod *et al.*, 2003:89). It also includes screening and preventative therapy for these conditions as well as the treatment of sexually transmitted diseases (STDs) such as syphilis and gonorrhoea (Council for Medical Schemes, 2009c:8). The four areas of preventative therapy that the medical schemes reported on to have been providing were: 84% of beneficiaries have access to screening for tuberculosis; 84% of beneficiaries have access to preventative therapy for tuberculosis; 87% of beneficiaries have access to preventative therapy for PCP; and 85% of beneficiaries have access to treatment for STDs (McLeod *et al.*, 2003:89).

According to Regensberg and Makiwane (2009:70) in AfA Clinical Guidelines, other programmes include prevention of mother-to-child transmission using a short course of AZT or a single dose of NVP to a pregnant mother and infant just before birth can significantly reduce or nearly eliminate paediatric infection. The medical schemes reported on these beneficiaries to MTCT benefits and stated that

- 41% of beneficiaries had access to AZT only;
- 56% of beneficiaries had access to AZT and 3TC or any other combination therapy;
- 55% had access to nevirapine; 84% had access to caesarean section; 47% to formula feeds; and
- 77% to MTCT counselling (McLeod *et al.*, 2003:91).

Other coverage included post-exposure prophylaxis (PEP), the provision of ARVs to those who may have been exposed to HIV in order to prevent infection in cases of: sexual assault, occupational injury (needle-prick injury); and other sexual exposure to HIV (National Department of Health, 2004:74).

2.3.3.3 Coverage of ART

ARV therapy is central to the management of HIV/AIDS (McLeod *et al.*, 2003:92). ARVs are expensive and largely unaffordable in developing countries like SA. In SA the treatment began in the form of one-drug regimen (monotherapy) (McLeod *et al*, 2003:92). Further research indicated that a combination of three drugs (triple-therapy cocktails) or HAART, is optimal (Regensberg & Makiwane, 2009:43; Bartlett *et al.*,

2006a:2051; Moyle & Back, 2001:105). According to AfA management programme the different kinds of ART include the following (Regensberg & Makiwane, 2005:7):

- Monotherapy, when one kind of HIV medicine is used alone. Not effective because it attacks HIV in one way (Regensberg & Makiwane, 2005:7).
- Combination therapy – using two or three drugs together to attack the HIV in more than one way.
- Triple therapy – with a combination of different drugs in one tablet.
- Highly Active Antiretroviral Therapy (HAART) - different ARVs combined to produce the best effects.

Currently there are six main classes of ARVs classified as HAART (Only five are discussed below) (De Clercq, 2009:308; Clarke *et al.,* 2008: HS-3; Marfatia & Smita, 2005:40):

- **Nucleoside reverse transcriptase inhibitors (NRTIs)** e.g. zidovudine (Retrovir®, AZT), didanosine (Videx®, ddl), zalcitabine (Hivid®, ddC), lamivudine (3TC®), stavudine (Zerit®, Stavir®®, Aspen-Stavudine®, d4T), abacavir (Ziagen®, ABC) Emtricitabine and Combivir® or Duovir® a combination of AZT and 3TC in one tablet.
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** e.g. nevirapine (Viramune®, NVP) and efavirenz (Stocrin®, EFV).
- **Protease inhibitors (PIs)** e.g. saquinavir (Invi-rase®, Forto-vase®, SQV), ritonavir, (Norvir®, RTV), indinavir (Crixivan®, IDV), nelfinavir (Vira-cept®, NFV), lopinavir/ritonavir (Kaletra®), amprenavir (Agenerase®), atazanavir (Reyataz®) and fosamprenavir (Lexiva® - USA, Telzir® - Europe).
- **Fusion inhibitors** – Enfuvirtide (Fuzeon®).
- **Chemokinase receptor**s (CCR5) – Maraviroc (Celsentri® - Europe, Selzentry® – USA).

2.3.3.4 Use of HAART in the management of HIV/AIDS

The entry of HIV into the human body leads to continuous high-level viral replication, immunosuppression, resistance (due to mutation) and persistence (due to entry of HIV in sanctuary sites and resting memory T-cells). HIV an incurable condition since HIV is a virus and not a condition. Thus life-long multi-drug therapy is required for near complete suppression of HIV-1 replication (Marfatia & Smita, 2005:40). In light of the above, a potent and effective combination ARV therapy for HIV referred to as HAART was introduced. HAART has revolutionised the management of HIV-1 infection. According to Chandwani and Shuter (2008:1023), ARV therapy has improved steadily in terms of efficacy, tolerability, and dosing convenience since the advent of HAART in 1995.

2.3.3.5 South African National ART Guidelines

In this section the South African National ART guidelines will be discussed with specific reference to regimens recommended for adults and children.

2.3.3.5.1 ART in adults

The recommended ARV regimens in adults are: first-line therapy – regimen 1 and second-line therapy – regimens 2 as shown in Table 2.9 (National Department of Health, 2004:7).

Table 2.9: Recommended regimens for naïve adult patients

Regimen	Drugs
1a	Stavudine (d4T) 40 mg every 12 hours (or 30 mg every 12 hours if < 60 kg) plus lamivudine (3TC) 150 mg every 12 hours plus efavirenz (EFV) 600 mg at night (or 400 mg if < 40 kg)
1b	Stavudine 40 mg every 12 hours (or 30 mg bd if < 60 kg) plus lamivudine 150 mg every 12 hours and nevirapine (NVP) 200 mg daily for 2 weeks, followed by 200 mg every 12 hours
2	Zidovudine (AZT) 300 mg every 12 hours with didanosine (ddl) 400 mg once a day (250 mg daily if < 60 kg), taken alone, dissolved in water on an empty stomach and lopinavir/ritonavir (LPV/r) 400 mg/100 mg every 12 hours

According to the South African National ART guidelines (National Department of Health, 2004:7), in non-naïve patients who have been exposed to ART in the past, an ARV expert has to be consulted before a treatment regimen is commenced. Those patients controlled on their ARV have to continue with their regimens. Those who have stopped for several reasons, but were controlled, could recommence therapy and be monitored. Those who had failed a previous regimen should be started on appropriate drugs they had not been exposed to before.

As of August 2006, there were over 20 approved ARVs, belonging to the HAART from which to design combination regimens (Bartlett *et al.*, 2006a:2051). Most clinical experience with combination therapy in treatment-naïve individuals is based on two different types of combination regimens, namely: NNRTI-based (1 NNRTI and 2 NRTI) and PI-based (1-2 PIs and 2 NRTIs) regimens (Bartlett *et al.*, 2006a:2051; National Department of Health, 2004:6). According to the AfA Clinical Guidelines (Regensberg & Makiwane,

2009:43), dual NRTIs form the backbone of all ARV combinations. The recommended dual NRTI combinations are shown in Table 2.10 (Regensberg & Makiwane, 2009:44).

Table 2.10: Dual NRTI combinations

Recommended combinations
Stavudine and lamivudine
Tenofovir and lamivudine
Zidovudine and lamivudine
Tenofovir and emtricitabine
Zidovudine and didanosine
Abacavir and lamivudine
Hazardous combinations - AVOID
Stavudine and didanosine
Tenofovir and didanosine
Antagonistic combinations – AVOID
Stavudine and zidovudine

These recommended regimen combinations are similar to the recommended regimens in the European region (WHO, 2009b:13), inclusive of the combinations that are not recommended for first-line ART as have also been confirmed by Barrios *et al.* (2005:569). In patients who are unable to tolerate NRTIs because of lactic acidosis, a combination of an NNRTI (efavirenz or nevirapine) with a booster PI is recommended by the AfA Clinical Guidelines as reported by Regensberg and Makiwane (2009:45). Since this combination presents a problem of DDIs, alterations of the PI dose (ritonavir-boosted PIs) is recommended. The recommended doses for PI-naïve and PI-experienced patients are shown in Table 2.11.

Table 2.11: Recommended doses for PIs and NNRTIs combinations for PI – naïve and experienced patients (Regensberg & Makiwane, 2009:45)

PI	Dose for PI-naïve		Dose for PI-experienced	
	Nevirapine	**Efavirenz**	**Nevirapine**	**Efavirenz**
atazanavir/ ritonavir	not recommended	400 mg/100 mg once a day	not recommended	400 mg/100 mg
darunavir/ ritonavir	standard dose	standard dose	standard dose	standard dose
lopinavir/ ritonavir	standard dose	standard dose	600 mg/150 mg twice a day	600 mg/150 mg twice a day
saquinavir/ ritonavir	standard dose	standard dose	standard dose	standard dose

2.3.3.5.2 Treatment of an adult patient with concomitant TB

According to the South African ART guidelines (National Department of Health, 2004:18), in a TB patient with no history of WHO stage 4 (refer to Section 2.3.2.1.1) illness, and a CD4 count > 200 cells/mm^3, it is not necessary to administer ART, and the patient continues with the TB treatment. If the patient has a history of WHO stage 4 illness, and/or CD4 count < 200 cells/mm^3, the patient has to complete a two months TB treatment before receiving ART. Where the CD4 count is less than 50 cells/mm^3, the patient should complete at least 2 weeks of TB therapy before initiating ART. The recommended regimens are shown in Figures 2.1 and 2.2 (National Department of Health, 2004:14).

Figure 2.1: Treatment of adult patients with concomitant TB while on ART

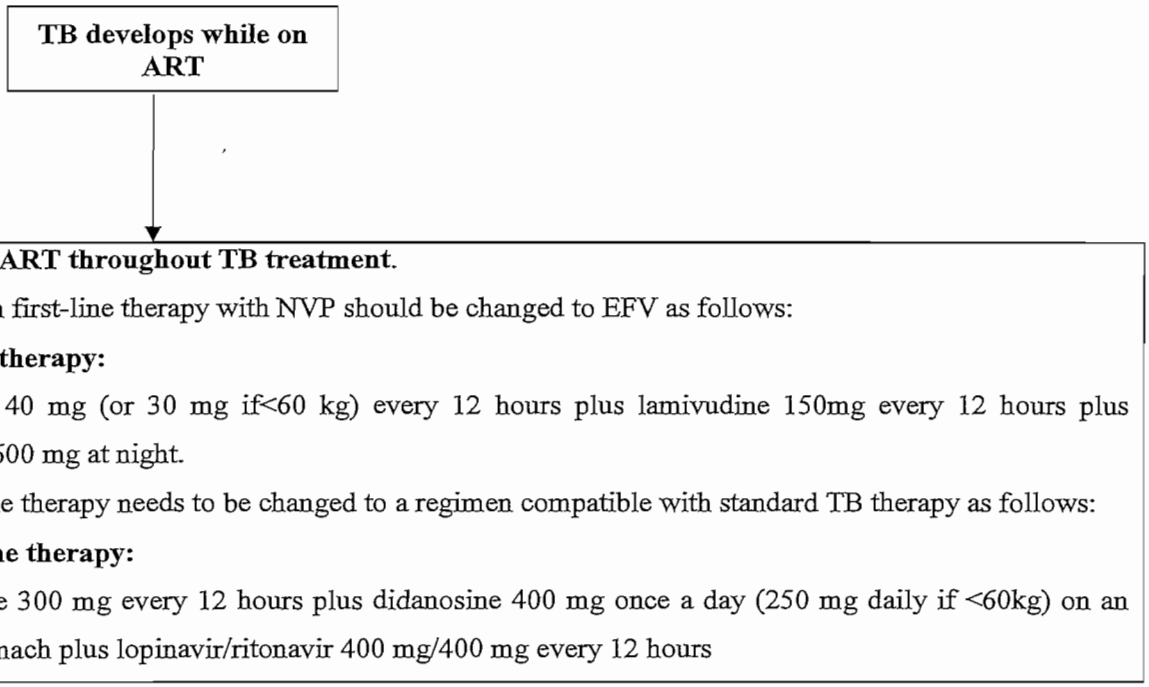
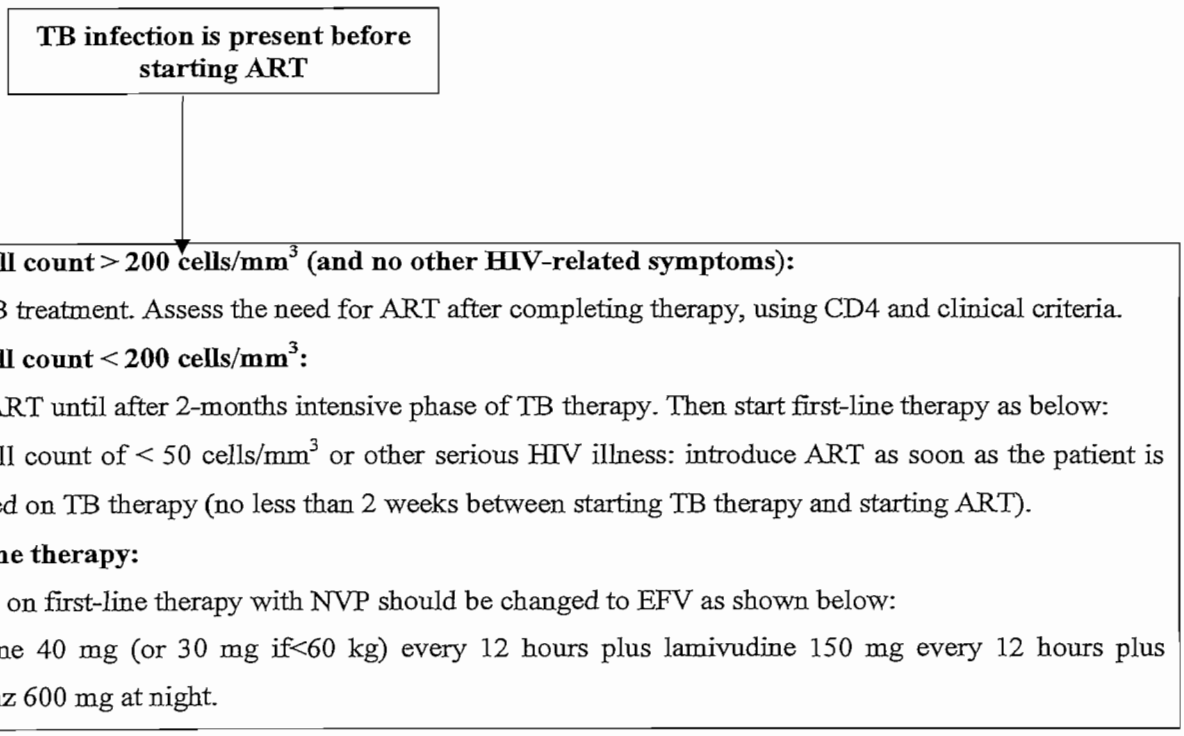


Figure 2.2: Treatment of adult patients with concomitant TB before starting ART



2.3.3.5.3 Treatment for pregnant women

According to Regensberg and Makiwane (2009:70) and the National Department of Health (2004b:33), there are different protocols for treating pregnant women depending on their condition:

- **Pregnant women with early stage HIV, or HIV not requiring ART:** The protocol is to follow the national PMTCT, and to provide co-trimoxazole prophylaxis to patients from stage 2 onwards.
- **Pregnant women who present with stage 4 or CD4 less than 200 cell/mm^3, irrespective of WHO stage:** Commence on first-line treatment with: stavudine 40 mg every 12 hours (or 30 mg every 12 hours if <60 kg) plus lamivudine 150 mg daily for 2 weeks, followed by 200 mg every 12 hours (efavirenz can be used post-partum if contraception is guaranteed after delivery or if the patient is sterilised).
- **Women who fall pregnant on ART**:

  Women on efavirenz: Counsel about possible teratogenicity in the first trimester. If pregnancy is continued, stop efavirenz and start nevirapine if in the first trimester. Discuss with ART specialist.

  Women on d4T and 3TC and nevirapine: Continue ART and do Alanine transaminase (ALT) monthly.

  Women on AZT and ddl and LPV/RTV: Continue ART, do full blood count and monitor sugar levels as appropriate.
- **HIV-infected pregnant women presenting after 35 weeks:** Defer ART, provide PMTCT, and review after delivery.

2.3.3.5.4 Recommended ART for children

The criterion for commencing ART in children is that the patients will have to meet both medical and psycho-social criteria before starting therapy.

Medical Criteria: Recurrent hospitalisation (> 2 admissions per year) for HIV-related disease, or prolonged hospitalisation or modified WHO stage 2 or 3 disease or CD4 percentage < 20% in a child under 18 months old irrespective of disease stage or CD4 percentage < 15% in a child over 18 months old irrespective of disease stage. The CD4 criteria for initiation of ART shown in Table 2.12 (National Department of Health, 2005:81) and the recommended ART guidelines in children are shown in Table 2.13 (National Department of Health, 2005:82).

Table 2.12: CD4 criteria for initiation of ART

Age	< 12 months	12 to 35 months	36 to 59 months	5 years and older
CD4 %	All	< 20	< 20	< 15
Absolute CD4 count		< 750	< 500	< 350

Table 2.13: Recommended regimens in children

Paediatric first – line therapy – Regimen 1		
	6 months – 3 years	**>3 years old and >10kg**
First – line	stavudine (d4T) lamivudine (3TC) lopinavi/ritonavir (LPV/RTV)	stavudine (d4T) lamivudine (3TC) efavirenz (EFV)
Paediatric second – line therapy – Regimen 2		
	6 months – 3 years	**>3 years old and >10kg**
First – line	zidovudine (AZT) DDI nevirapine (NVP)	zidovudine (AZT) DDI lopinavi/ritonavir (LPV/RTV)

A summary of the recommendations on when to start ART according to AfA Clinical Guidelines as reported by Regensberg and Makiwane (2009:83) and the National Department of Health (2005:82):

Infants: either 2 NRTI[1] and 1 PI (Lopinavir) or 2 NRTI[1] and 1 NRTI (nevirapine) Not to be used if mother or infant received single-dose nevirapine as part of strategy to prevent mother-to-child transmission.

Children: either 2 NRTI[1] and (lopinavir) or 2 NRTI[1] and NNRTI (efavirenz or nevirapine[2]).

[1]*Dual NRTI combination recommended: abacavir plus lamivudine; zidovudine plus lamivudine. Stavudine and didanosine are no longer preferred in first-line therapy due to concerns of toxicity.*

[2]*Nevirapine is the preferred NNRTI for children under the age of three years, efavirenz is only registered for children over three years. Didanosine must be taken alone, on an empty stomach, at least an hour before (or 2 hours after) a meal. The tablets should be dissolved in an at least 30 ml of water. The doses are given per weight or body surface area.*

2.3.3.5.5 Treatment for children with concomitant TB

There are two protocols depending on whether the child developed TB while on ART or developed the infection before ART initiation. These are shown in Figures 2.3 and 2.4 (National Department of Health, 2005:85).

Figure 2.3: Treating a child who develops TB while on ART

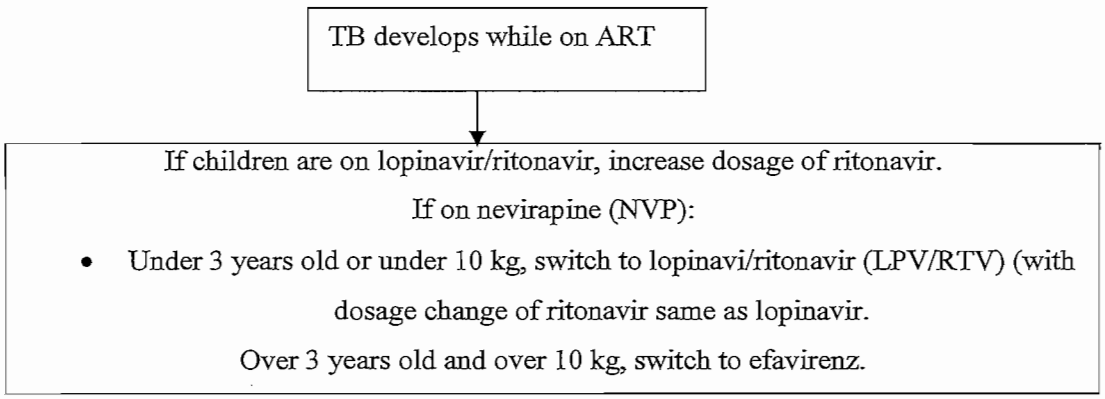
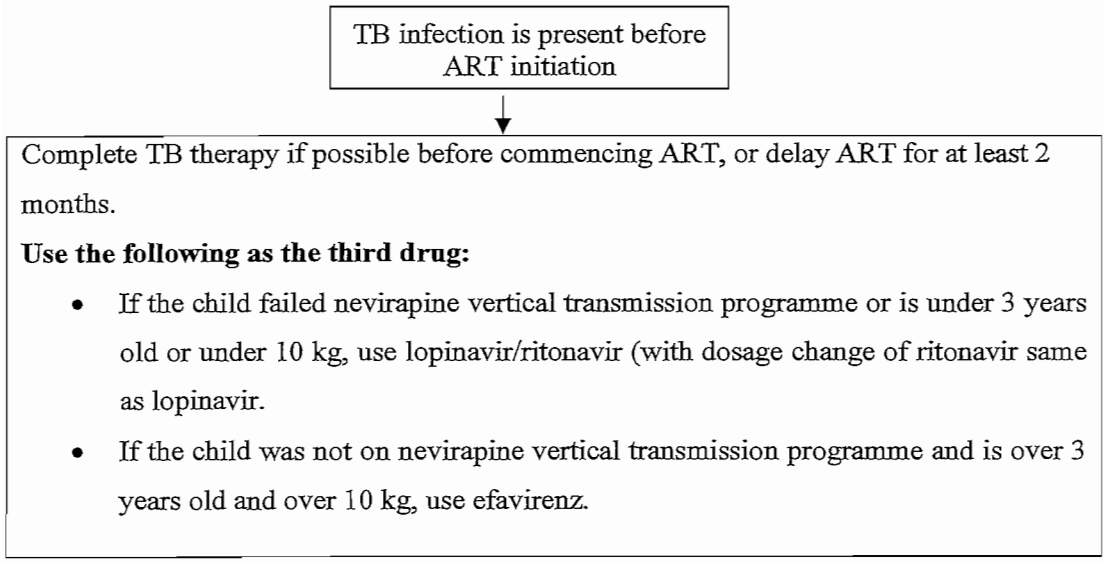


Figure 2.4: Treating a child with TB infection before ART initiation



2.3.3.5.6 Potential for DDIs in the recommended regimens

Many ARV drugs used to treat HIV infection, particularly the PIs and NNRTIs interact with other ARVs (Miller *et al.*, 2007:1379; McNicholi & Coffey, 2009; Faragon & Piliero, 2004). DDIs may arise between ARVs because of the pharmacokinetics or pharmacodynamics of the administered ARVs. They are the therapeutic drugs most at risk of DDIs because there are potent inhibitors or inducers of liver enzymes, such as the cytochrome P450 isoenzymes (CYP450), which metabolise many other drugs (Seden *et al.*, 2009:5). HAART consists of different groups that are PIs, NRTIs and NNRTIs (Clarke *et al.*, 2008:HS-3; Young, 2005:286; Winston & Boffito, 2005:1)

DDIs commonly found between PIs and NNRTIs are due to the hepatic metabolic pathways, as compared to those that occur in NRTIs that are due to competition for renal tubular secretion (Young, 2005:288; Cohen *et al.,* 2002:42). According to Miller *et al.* (2007:1379), clinically significant DDIs are more likely in regimens that contain PIs than those that contain NNRTIs. Furthermore, it has been reported that treatment of TB in patients on ART is complicated by toxicity, malabsorption, DDIs and immune reconstitution paradoxical reactions (Naomi & Lee, 2004:337). It has also been reported by Regensberg and Makiwane (2009:42) that rifampicin has significant drug interactions with PIs and NNRTIs. It is therefore preferably recommended to use regimens that do not interact significantly with rifampicin for example the NRTIs (Seden *et al.*, 2009:6; Winston & Boffito, 2005:2; Young, 2005:294; Cohen *et al.*, 2002:45).

2.3.4 Recommended ART Guidelines in other countries

In this section, recommended ARV treatment guidelines from other countries will be discussed showing some similarities and differences in comparison with the South African ART recommended guidelines.

2.3.4.1 European region

According to the HIV/AIDS treatment and care clinical protocols for the WHO European Region (WHO, 2009a:13), in the first-line HAART regimen, it is recommended that 2 NRTIs and 1 NNRTI be combined as shown in Table 2.14 (WHO, 2009a:13). According to their regimens one of the NRTI should be 3TC or emtricitabine, then the second NRTI should be AZT. When comparing this regimen with the South African first-line regimen, AZT is used as a second-line therapy once the first-line has failed (National Department of Health, 2004:6).

Another difference with this protocol is that stavudine is used as first-line therapy in SA (National Department of Health, 2004:6). Yet the European region has moved away from recommending it for initial treatment because of its poor toxicity profile and a study reported its higher rate of long-term side-effects (Shah *et al.*, 2003:131). Another difference in their regimen is using tenofovir or abacavir in combination with 3TC (WHO, 2009a:13) which is not used in SA (National Department of Health, 2004:6). It has been reported that a combination of tenofovir/amtricitabine (TDF/FTC) is superior to a combination of AZT/3TC when used in combination with efavirenz due to a lower rate of side-effects in the TDF arm (Gallant *et al.*, 2006:251).

Table 2.14: Recommended first-line HAART in European region

ARV drug classes	HAART regimens
2 NRTIs and 1 NNRTI	AZT and 3TC and (**EFV**[a] or NVP) or TDF and FTC and (**EFV**[a] or NVP) or ABC and 3TC and (**EFV**[a] or NVP)

[a] *EFV is highlighted as the preferred NNRTI.*

For second-line HAART regimen in the European region, the use of the PI is highly recommended (WHO, 2009a:19) like in the South African treatment guidelines (National Department of Health, 2004:6). Another similarity is that in the PI class, the majority of drugs are boosted with a low dose of ritonavir 100 mg twice a day. Like in SA LPV/r is the PI of choice due to its well-documented potency and relatively low tablet burden and good tolerance (Kessler *et al.*, 2003) and a new tablet formulation of LPV/RTV has been approved in Europe requiring two pills twice a day and no refrigeration (WHO, 2009a:20).

2.3.4.2 North America

With the implementation of strategies to prevent perinatal HIV-1 transmission, in North America, the epidemiology of perinatal HIV-1 has changed drastically, using zidovudine as PEP with a reduction in the risk of HIV infection by approximately 81% (PHTF, 2007:15). It is a priority to identify HIV-1 infection of the mother before or during pregnancy and even during labour or at birth so as to prevent perinatal transmission and for care of the mother of the HIV-exposed infant (CPS, 2004:409). In North America, most HIV-1-infected pregnant women receive care for HIV infection during the prenatal period receiving combination ART with three or more drugs (CPS, 2004: 412), as shown in the Table 2.15.

Comparing this protocol with the South African one, a single dose of nevirapine is given at the onset of labour and to the neonate as soon as possible after birth (National Department of Health, 2005:11). The same applies to the North American protocol (PHTF, 2007:10). Pregnant women meeting the criteria for initiation of ART do receive triple therapy. The non-breastfeeding women receive a combination of AZT and NVP.

In North America, pneumocystis pneumonia (PCP) is the most common serious opportunistic infection in HIV-1-infected children. The following regimen is instituted, as per US Public Health Service, Infectious Diseases Society of America, prevention of opportunistic infections working group (USPHS/IDSA, 2004).

- Trimethoprim 150 mg/m^2/day with sulfamethoxazole 750 mg/m^2/day PO at a schedule of twice daily for 3 days/week.

- Dapsone 2 mg/kg PO once daily and 4 mg/kg PO once weekly.
- Pentamidine 4 mg/kg IV every 2 to 4 weeks.
- Atovaquone – Infants 1 to 3 months of age: 30 mg/kg PO once daily and infants 4 to 24 months of age: 45 mg/kg PO once daily.

Table 2.15: Maternal intrapartum and infant prophylactic ARV drug regimens when an HIV-1-infected mother has not received prenatal ART

Drug	Maternal dosing, intrapartum	Infant dosing	Infant schedule
NVP	Single 200 mg oral PO dose at onset of labour	Single 2 mg/kg PO dose	Single dose at 48 h -72 h
ZDV and 3TC	ZDV, 600 mg PO at onset of labour followed by 300 mg PO every 3 h until delivery; and 3TC, 150mg PO at onset of\ labour followed by 150 mg PO every 12h until delivery	ZDV, 4 mg/kg PO every 12h; and 3TC, 2 mg/kg PO every 12h	For 1 week
ZDV	2 mg/kg bolus followed by continuous infusion of 1 mg/kg/h until delivery	2 mg/kg PO 4 times/day if unable to tolerate oral therapy, 1.5 mg/kg IV every 6 h if infant is preterm, 1.5 mg/kg every 12h for 2 weeks and then increase to 2mg/kg every 8h	Beginning 8 h – 12 h after birth and continuing through 6 weeks of age
ZDV with NVP	ZDV, 2 mg/kg IV bolus followed by continuous infusion of 1mg/kg/h until delivery; and NVP, single 200 mg PO dose at onset dose at onset of labour	ZDV, 2 mg/kg PO 4 times/day; and NVP, single 2mg/kg PO dose	Start ZDV beginning 8h-12h after birth and continue through 6 weeks of age; and single dose of NVP at 48h-72h of age

IV = Intravenous; PO = oral

In SA the treatment for PCP is such that co-trimoxazole is given as a single strength (480 mg) tablet per 4 kg body weight (National Department of Health, 2004:16). All hypoxic patients are given adjunctive prednisone 40 mg twice daily for days 1 to 5, 40 mg daily for days 6 to 10 and 20 mg daily for days 11 to 21

(Regensberg & Makiwane, 2009:29). Unlike in North-America, in SA there are extremely limited options for patients with co-trimoxazole intolerance. According to AfA Clinical Guidelines (Regensberg & Makiwane, 2009:25), pentamidine, trimethoprin (given with dapsone) and primaquine (given with clindamycin) are no longer registered in SA.

2.3.4.3 United Kingdom

In the United Kingdom (UK), epidemiological data showed that almost one-third of the patients with HIV infection remain undiagnosed (Gazzard, 2008:570). According to 2008 British HIV Association Guidelines for HIV-1 infection, the following recommendations were made to treat HIV-1 infection in adults (Gazzard, 2008:570):

- Efavirenz is considered first-line in all patients (level 1b).
- Boosted PIs are to be reserved for specific groups of patients.
- Nevirapine to be reserved for women wishing to become pregnant and patients with mental health problems.
- Travada to be the first choice for nucleoside backbone to be used with efavirenz.
- Combivir to be used in patients to prevent mother-to-child transmission (level 1b) (Gazzard, 2008:571).

When comparing the UK guidelines with the SA guidelines, it is observed that efavirenz in SA is also used as a first-line therapy in the initial stage in regimen 1a. Studies performed on efavirenz showed the superiority of this drug over the unboosted PIs (Shafer *et al.*, 2003:2304; Bartlett *et al.*, 2006b:284).

2.3.4.4 Ethiopia

According to 2007 estimates in Ethiopia, the national adult HIV prevalence was reported to be 2.1% (7.7% in urban and 0.9% in rural areas) (Federal Ministry of Health, 2007:2). A report from the Federal HIV Prevention and Control Office (Federal Ministry of Health, 2007:2) of Ethiopia, stated that in 2007, the number of people living in Ethiopia with HIV/AIDS was 977 393 (41% males and 59% females), with an estimated 75 420 HIV-positive women. The highest prevalence occured in the 15 to 24 age group and in both urban and rural areas, the prevalence was higher among females than males. Ethiopia has a challenge of more than 90% paediatric AIDS due to vertical virus transmission from mother to child. Therefore their PMTCM programmes provide for both prevention of HIV transmission from mother to child and enrolment of infected pregnant women and their families into ART.

Therefore the objectives of the PMTCT services in Ethiopia include the following (Federal Ministry of Health, 2007:2):

- Promote primary prevention of HIV amongst women and men of reproductive age.
- Reduce and ultimately eradicate new paediatric HIV infection.
- Promote access to HIV and ART for HIV-infected pregnant women and their families.
- Reduce HIV-related morbidity and mortality of HIV-infected mothers through care, thereby preserving the family unit and reducing the incidence of orphans.
- Promote access of HIV-exposed infants to care.
- Address family planning

The basic principles for the use of ARV drugs for PMTCT in Ethiopia as stated by the Federal Ministry of Health (2007: 26) were as follows:

- ART was in use of 3 or more ARVs simultaneously to treat HIV infection. ART being a life-long treatment for the mother and could also significantly reduce MTCT.
- ARV prophylaxis – short term use of ARV drugs in the mother and/or infant to reduce MTCT.

In Ethiopia, HAART is indicated based on WHO clinical staging and/or CD4 count as follows:

- If CD4 testing is available:
  - WHO Stage 4 disease irrespective of CD4 cell count.
  - WHO Stage 3 with CD4 cell count <350 cells/mm^3,
  - WHO Stage 1 or 2 disease with CD4 cell count $\leq$ 200 cells/mm^3.
- If CD4 count is not available:
  - WHO Stage 4 disease irrespective of total lymphocyte count.
  - WHO Stage 3 irrespective of total lymphocyte count.
  - WHO Stage 2 disease with a TLC $\leq$ 1200 cells/mm^3 (Federal Ministry of Health, 2007:26).

In SA the guidelines for starting ART in adults as compared to the Ethiopian guidelines, emphasise that the patient must be ready for treatment and must have a WHO stage 4 condition or other serious morbidity or two CD4 counts below 350 cells/mm^3 done at least six weeks apart (Regensberg & Makiwane, 2009:41).

The principles for the use of ARVs for PMTCT as stated by the Federal Ministry of Health in Ethiopia (2007:27) are as follows:

- **ARV treatment for HIV-infected women who become pregnant while receiving HAART**: Women receiving an EFV-containing regimen and in the first trimester of pregnancy, NVP must be substituted for EFV. Women to continue their HAART during labour and post partum. Infants born to such mothers to receive AZT 4 mg/kg/dose twice daily for 7 days.

- **ARV treatment for HIV-infected pregnant women eligible for HAART and their infants:** Start ART if mother has advanced HIV infection or a CD4 count < 200 cells/mm^3. EFV is contraindicated as well as dual NRTIs, d4T and ddI. Infants born of such mothers to receive PEP with AZT for seven days.
- **ARV prophylaxis for HIV-positive pregnant women not eligible for ART and their infants.** Start from 28 weeks of pregnancy with short course of ARV prophylaxis. Single drug prophylaxis with nevirapine for the mother and baby is complete.

These recommendations are similar to the South African ones; the only difference is that in SA for pregnant women with early stage HIV, or HIV not requiring ART, co-trimoxazole prophylaxis is administered to patients from stage 2 onwards (National Department of Health, 2004:23). It is also stated in the South African guidelines that breastfeeding increases the risk of transmission and therefore should be discouraged (Regensberg & Makiwane, 2009:71).

2.3.4.5 Germany and Austria

The German-Austrian recommendations as published by Holzapfel publishers (Anon., 2003:261) ART for HIV infection stated that in the initial therapeutic regimen, in addition to viral load and stage of disease, there were other factors to consider such as lifestyle, co-morbidity, and additional co-administered therapies to be considered when selecting the initial drug combination. The options to consider were:

- Combination of one, or if necessary a boosted PI with two NRTI.
- Combination of a NNRTI with 2 NRTIs.
- Combination of 3 NRTIs.

These guidelines differ from the South African guidelines in that the initial therapy for ARV in HIV patients in SA consists of: 2NRTIs and 1 NNRTI; 2 NRTIs and 1 PI. According to Murphy *et al.* (2001:F2), it may make sense to employ more than three drugs in the initial therapy (e.g. a PI boosting with ritonavir), although some experts favour the primary use of four drug substances for patients at high risk of virological failure.

2.3.4.6 Uganda

According to Omaswa, the then Director General of Health Services in Uganda, HIV/AIDS remained a major cause of death among adults and children despite the declining trends of HIV/AIDS (Ministry of Health, 2003: X). The number of people living with HIV/AIDS in Uganda has continued to rise. It was estimated in 2003 that over one million people (of which about 100 000 children under the age of 15 years) were infected and probably over one million have already died from HIV disease (Ministry of Health, 2003:X).

In Uganda it was declared that a US Drug Regulatory Agency, Food and Drug Administration (FDA) by July 2003 had approved 19 ARV agents for the treatment of HIV-1 infection (Ministry of Health, 2003:9). These FDA regimens were: seven NsRTIS, 1 NtRTI, 3 NNRTIs and 8 PIs (Ministry of Health, 2003:9). Comparing their regimens with the SA regimens, the difference is that in SA there are 5 NsRTIs, 2 NNRTIs and 7 PIs. Amtricitabine in SA is only available in combination with Tenofovir as Truvada (Regensberg & Makiwane, 2009:40).

In Uganda it is recommended to initiate ARV therapy in adults and adolescents with documented HIV infection and (Ministry of Health, 2003:11):

- WHO Stage 4 disease irrespective of CD4 cell count.
- Advanced WHO Stage 3 disease including persistent or recurrent oral thrush and invasive bacterial infections irrespective of CD4 cell count or total lymphocyte count.
- When CD4 testing is available, ART could be started for patients in WHO stages 1, 2 or 3 with CD4 cell counts ≤ 200 cells/mm^3.
- Tuberculosis and a CD4 cell count between 200 cells/mm^3 to 300 cells/mm^3.

As compared to the South African guidelines for starting ART in adults, the patients must be ready for treatment and the patient must have a WHO stage 4 (except for TB) and other serious morbidity or two CD4 counts below 350 done at least six weeks intervals (Regensberg & Makiwane, 2009:41). In SA, TB per se, is not used as an indication to start ART (even if it is extrapulmonary TB, which is WHO stage 4) because TB occurs with a very wide spectrum of immune deficiency in countries with a high TB incidence. In SA the commencement of a TB patient on ART is guided by the following CD4 count: CD4 $>$ 350 cells/mm^3, CD4 200 cells/mm^3 to 300 cells/mm^3 and CD4 $<$ 200 cells/mm^3 (Regensberg & Makiwane, 2009:42). Furthermore and interesting, in Uganda, if a patient meets the ART initiation criteria, certain patient-specific factors had to be considered before starting ARVs. These were according to the Ugandan Ministry of Health (2003:11):

- Interest and motivation in taking therapy.
- Presence of co-morbidities.

- Psychosocial barriers.
- Financial barriers.
- Potential for adherence.
- A patient should not be anaemic with HB below 8g/dl neither have symptomatic liver or kidney disease nor be on chemotherapy for non-HIV related cancers.

The following are guidelines on when to start ART therapy in infants and older children as shown in Table 2.16 (Ministry of Health, 2003:14).

Table 2.16: Recommendations for initiating ART in children in Uganda

Age	Diagnosing HIV Infection	Recommendation for ART
< 18 months	1. Clinical assessment **Plus** 2. Positive HIV test or history in the mother **Optional** 3. PCR-DNA if available 4. $_{P}$24 Ag if available	1. WHO Paediatric Stage 3 (AIDS) irrespective of CD4 cell % 2. Advanced Paediatric Stage 2 3. WHO Paediatric Stage 1 or 2 with CD4 cell < 20%
>18 months	1. Clinical assessment 2. Positive HIV test	1. WHO Paediatric Stage 3 2. Advanced Paediatric Stage 2 with no CD4 count 3. WHO Paediatric Stage 1 disease (asymptomatic) or Stage 2 with CD4 cell < 15%.

Comparing the Ugandan selection criteria for commencing ART in children with the South African, one criterion that is emphasised in SA is the medical criteria of recurrent hospitalisation (more than 2 admissions per year) for HIV-related disease, or prolonged hospitalisation (more than 4 weeks). The modified WHO Stage should be ¾ not stage 1 disease as for Uganda (National Department of Health, 2005:82). The rest of the criteria are similar.

The recommended first-line ARV regimens in adults and adolescents are shown in Table 2.17. Fixed combinations are also recommended as they may be cheaper, more user friendly and would facilitate better adherence because of low pill burden. These are recommended at national level to cover the majority of the patients in Uganda (Ministry of Health, 2003:15).

Table 2.17: Recommended first-line ARV regimens in adults and adolescents in Uganda

Regimen	Pregnancy and TB Consideration
ZDV/3TC and NVP or EFV **OR** D4T/3TC and NVP or EFV	Give NVP in pregnant women or women to whom effective contraception cannot be assured. Give EFV to patients requiring simultaneous ARV treatment and TB therapy containing rifampicin.

Comparing the above regimen with the South African first-line therapy regimen 1, because of drug resistance leading to vilogical failure, AZT does not form part of the ARV combination; it is given as a second-line treatment failure after first-line therapy (National Department of Health, 2004:6). Otherwise like in SA 1 NNRTI either EFV or NVP as a third drug is the recommended first-line regimen. The recommended second line of ART regimen in adults is shown in Table 2.18 (Ministry of Health, 2003:16). For economic reasons and simplicity of administration, only LPV/RTV was recommended as the PI for second-line for treatment failure.

Table 2.18: Recommended second-line ARV regimens in adults and adolescents in Uganda

First-line Regimens	Second-line Regimens for treatment failure
ZDV/3TC and NVP or EFV d4TC/3TC and NVP or EFZ	d4T/ddl and LPV/RTV ZDV/ddl and LPV/RTV

As observed in Table 2.18, d4T in Uganda is used as the second-line regimen for treatment failure as compared to the South African regimens; d4T is used as first-line regimen (National Department of Health, 2004:15). Another difference in the regimens is that in SA, AZT is used as a first-line therapy as compared to the Ugandan regimens where it is used as a second-line regimen for treatment failure (Ministry of Health, 2003:16). The similarity in both countries is that LPV/RTV is the only recommended PI for second-line regimen for treatment failure.

The recommended first- and second- line ART for infants and children are indicated in Table 2.19 (Ministry of Health, 2003:17).

Table 2.19: Recommended first- and second-line ARV regimens in children and infants in Uganda

First-line Regimen	Comments	Second-line regimens for treatment failure	Alternative second- line regimens for treatment failure
ZDV/3TC and NVP or EFZ **OR**	If < 3 years or < 13 kg, use NVP	d4T/ddl and LPV/RTV	d4T/ddl and NFV
d4T/3TC and NVP or EFV	If ≥ 3 years or ≥ 13 kg, use NVP or EFV	ZDV/ddl and LPV/RTV	ZDV/3TC and NFV

There are differences in the ARV choices for children in both countries. In Uganda as observed in Table 2.19 the age of the child has to be < 3 years as compared to SA age which is 6 months up to 3 years (National Department of Health, 2005:82). Another difference is the weight of children which is 13 kg for Uganda and 10 kg for SA. As for the regimens, in Uganda, AZT forms part of first-line therapy (Ministry of Health, 2003:17) while in SA AZT is used as second-line regimen for treatment failure (National Department of Health, 2005:82). Another difference in the regimens for both countries is that in SA EFV is used in children of age more than 3 years (National Department of Health, 2005:82) while in Uganda it is used in children ≥ 3 years, and for NVP if the age is more than 3 years, while in Uganda the age is ≥ 3years (Ministry of Health, 2003:17). While d4T is used as first-line therapy in SA (National Department of Health, 2003:82), in Uganda it is used as both first-line and second-line therapy (Ministry of Health, 2003:17).

2.3.4.7 United States of America

According to the PHTF (2008:1), recommendations for the screening and treatment of pregnant women and prophylaxis for perinatal HIV transmission has evolved considerably in the United States of America over the last 25 years, reflecting changes in the HIV/AIDS epidemic. Treatment of HIV infection in general and during pregnancy has evolved with an increasing number of women receiving HAART, throughout pregnancy. The USA recommendations towards prevention of HIV perinatal transmission were as follows (PHTF, 2008:4):

- The prevention of perinatal HIV transmission, combined antepartum, intrapartum, and infant ARV prophylaxis were recommended.
- Combination antepartum ARV drug regimens were considered more effective than single-dose regimens in reducing perinatal transmission.

- Longer duration of antepartum ARV prophylaxis (e.g. starting at 28 weeks gestation) was more effective than shorter duration (starting at 36 weeks gestation).
- Intrapartum combined with infant ARV prophylaxis to be given to reduce the risk of perinatal transmission.
- Postnatal infant ARV prophylaxis was recommended with a minimum period of 6 weeks.
- The addition of single-dose intrapartum/newborn NVP to the standard antepartum combination ARV regimens used for prophylaxis or treatment in pregnant women was not recommended because it does not appear to provide additional efficiency in reducing transmission and may be associated with the development of NVP resistance.

2.3.4.8 Tanzania

In the report by the permanent secretary for the Ministry of Health (2005: X11) in Tanzania, in 2003, it was stated that since the recognition of HIV/AIDS in Tanzania, the country responded by formulating and implementing a series of strategic plans and interventions to curb the epidemic. Despite all the efforts, the epidemic grew in both rural and urban communities, resulting in more than 2 million people living with HIV and AIDS and close to 800 000 cumulative AIDS cases in 2005 (Ministry of Health, 2005:87). This prompted the government to launch a National Care and Treatment Plan in the health sector strategy for HIV and AIDS, with the purpose of providing ARV treatment to as many people living with HIV/AIDS as possible (Ministry of Health, 2005:88).

According to the national guidelines for the clinical management of HIV/AIDS in Tanzania, the use of single drugs is not recommended and regimens are recommended for patients based on their clinical condition, lifestyle and ability to tolerate the regimen (Ministry of Health, 2005:94). A triple therapy consisting of 2 NRTI and 1 NNRTI or 2 NRTI and 1 PI is recommended. Below are the recommended first-line drug combinations in Tanzania as per the National Guidelines for the Clinical Management of HIV/AIDS (Ministry of Health, 2005:94-95).

The first-line ARV combination regimen for adults and adolescent ART naive patients:

The ministry of health recommends four different combinations of drugs for adults and adolescents, and these combinations are used according to indications and contraindications (Ministry of Health, 2005:95).

- Stavudine and lamivudine and nevirapine fixed dose combination (FDC) for example triomune 30 or 40 depending on the body weight < or > 60 kg, respectively.
- Zidovudine and lamivudine and nevirapine.
- Stavudine and lamivudine and efavirenz.

- Zidovudine and lamivudine and efavirenz.

In summary patients in Tanzania commence therapy on d4T and 3TC and NVP; however patients can be started on:

- AZT and 3TC and NVP if there is peripheral neuropathy.
- d4T and 3TC and EFV if there is TB and anaemia < 7.5 gn/dl.
- AZT and 3TC and EFV if there is TB, no anaemia (Ministry of Health, 2005:95).

When there are treatment failures, there is a need to change ART, and the general clinical recommendation in Tanzania is that when changing a patient's regimen due to toxicity, only the toxic drug(s) should be replaced, if possible. Therefore the first-line of the National ART programme includes the following ARV drug combinations with some common toxicity switches (Ministry of Health, 2005:99):

Table 2.20: Common toxicity switches for the first-line drugs in Tanzania

First-Line Regimen	Problem	Substitution
d4T and 3TC and NVP	Hypersensitivity due to NVP	d4T and 3TC and EFV*
d4T and 3TC and NVP or EFV*	Severe peripheral neuropathy due to d4T	AZT and 3TCand NVP or EFV*
AZT and 3TC and NVP or EFV*	Anaemia due to AZT	d4T and 3TC and NVP or EFV*
d4T and 3TC and NVP or EFV*	Intolerant to NVP and EFV	dT4 and 3TC and LPV/RTV**

* *Only if patient is older than 3 years of age and a woman with no risk of pregnancy.*

** *Follow-up liver function tests (LFTs) closely.*

As observed in Table 2.20, for Tanzania, for the first-line regimen it is recommended that four different combinations of drugs for adults and adolescents be used, as compared to the two ART regimens as recommended for use in SA (Ministry of Health, 2005:95 & National Department of Health, 2004:6). The initial ART regimen is d4T/3TC/NVP as compared to the SA first-line therapy which is d4T/3TC/EFV. It is not clear whether reliable contraception in women of child-bearing age is ensured when every patient has commenced on NVP.

As also observed in Table 2.20, the substitution drugs act as their second-line regimen for treatment failure as compared to the South African second-line therapy for patients who continue to fail virologically despite

demonstrating adherence. Furthermore didanosine (ddl) is not included in any of their regimens as compared to the South African recommended regimens but only used as a the recommended second-line regimen for pregnant women (Ministry of Health, 2005:96) . Therefore the recommended second-line regimen for pregnant women is: abacavir (ABC) and didanosine (ddl) and saquinavir/ritonavir (SQV/r or nelfinavir (NFV) (Ministry of Health, 2005:96).

The first-line regimen for pregnant women in Tanzania is AZT and 3TC and NVP as compared to the South African first-line therapy which is d4t and 3TC and NVP. In SA women who fall pregnant on ART and have been using AZT, continue with ART with the regimen as AZT and ddl and lopinavir/ritonavir (Ministry of Health, 2005:95; National Department of Health, 2004:23).

2.3.5 Adherence to ART

The goal of ART in patients with HIV/AIDS is to achieve maximum inhibition of HIV replication, reverse immunosuppression, minimise the development of viral drug resistance and to achieve sustained durability of treatment (Katlama *et al.,* 2004:217). One of the barriers to achieve this goal is suboptimal adherence to therapy. This can lead to development of viral resistance or cross resistance to a single ARV drug or a drug class, which can lead to loss of treatment efficacy (Hardy, 2005:247).

Adherence to ART as stated by Chesney (2006:S149) has been strongly correlated with HIV viral suppression, reduced rates of resistance, an increase in survival, and improved quality of life of the infected patient. Adherence poses a special challenge to both patient and the health care team, because HIV/AIDS being a chronic disease that requires lifelong therapy, patients start therapy when generally in good health, feel well, and demonstrate no obvious signs or symptoms of HIV/AIDS disease. Therefore continued commitment is required from both the patient and the health care team as stated by the Department of Health and Human Service (DHHS, 2008:108).

Adherence to ART in SA is significantly influenced by the social, historical, cultural and geographical context of HIV/AIDS (Gibert & Walker, 2009:1123). According to Marks (2008:37), AIDS was an epidemic waiting to happen; the regions' complex social history has compounded the way in which the epidemic has unfolded over the past three decades. Expectation of poor adherence is a major concern in expanding therapy to South Africans, because many of them live in severe poverty (Harries *et al.*, 2001:410).

2.3.5.1 Predictors of poor adherence to ART

Adherence to ART is an essential component of individual and treatment success. According to Schneider *et al.* (2007:1096), it is related to the patient's characteristics, the regimen, and the setting of the clinic. Factors that have been associated with poor adherence include:

- low levels of literacy (Marcus, 2006:339);
- certain age-related challenges (e.g. vision loss, cognitive impairment) (Van Eijken *et al.,* 2003:229);
- psychosocial issues like depression, homelessness, lower social support, stressful life events, dementia (Halkitis *et al.*, 2005:345);
- difficulty with medication taking (e.g., trouble with swallowing the pills);
- stigma (Carr & Gramling, 2004:30);
- complex regimens (Bangsberg, 2006:939);
- adverse drug events (Chesney, 2006:S149); and
- life-long nature of the treatment and treatment fatigue (Hardy, 2005:247).

From all the above factors, adherence is indeed a challenge, therefore approaches to improve adherence should be sought and tailored to the patients' lifestyle.

2.3.5.2 Interventions to improve adherence to ART

It is the responsibility of all health care providers who care for HIV/AIDS to undertake the following strategies to improve and sustain adherence to treatment with ARV drugs:

- Patient-related strategies that include:
  - Health care workers to individualise treatment with patients' involvement in making decisions about the treatments (Chesney *et al.,* 2000:1599).
  - Negotiate a treatment plan that the patient understands and to which she/he commits (Spine *et al.*, 2002:1481) and family members to be recruited to become participants in the plan of treatment.
  - Patient's "readiness" to be on the lifelong medication to be clearly established (Tesoriero *et al.*, 2003:484).
  - Patients to understand that the first ART regimen has the best chance of long-term success (Mannheimer *et al.*, 2006:S41).

- Clinician and health team strategies that include:

- Building a trusting relationship with patients over time and maintaining good communication that would improve on adherence and long-term outcomes. Health care workers displaying attitude and behaviour that are supportive and non-judgemental and that will encourage the patients to be open about their adherence and problems they are experiencing with the treatment (McPherson-Baker *et al.*, 2000:399).
- Monitoring and encouraging adherence at every clinical encounter (Stanic & Grana, 2009:47).
- Explaining possible side-effects when initiating therapy (Tesoriero *et al.*, 2003:484).

- Regimen-related strategy
  - Regimens to be simplified by reducing the number of pills and frequency of taking drugs. According to a study published by Paterson *et al.* (2000:21), an adherence rate of 95% was demonstrated to correlate best with superior virological outcomes in patients treated with PI-based therapy.
  - Minimising drug interactions and side-effects through rational drug selection (Lu *et al.,* 2008:86)
  - Minimising differences between medication requirements e.g. with/without food. A survey by Moyle (2003:34), of HIV-positive patients receiving HAART indicated a preference for ARV regimens that could be taken once daily, involving few pills and do not have specific diet restrictions.

2.3.5.3 Methods used to measure adherence

There are several methods that can be employed to measure adherence and these include (Hardy, 2005:247; Orrell *et al.*, 2003:1369):

- Patients' self-report as reported by Moatti *et al.* (2004:S55), that adherence should be a changing behaviour driven by patient's experience.
- Tablet counts.
- Evaluation of pharmacy refill patterns.

It should be noted that none of these methods should be considered a single. The best approach is to adherence measurements, as they may either overestimate or underestimate a patient's adherence to ART.

2.4 OVERVIEW OF DDIs

This section contains a discussion of DDIs, starting with the concept of DDIs, types, mechanisms, dynamics, rating system and possible causes. Thereafter, a discussion on prevalence of DDIs, and consequences in clinical practice will follow. Then the pharmacological aspects of DDIs in ARV agents, the risk factors for DDIs with ARVs, the role of pharmacists in detecting and preventing DDIs in clinical practice will be discussed. Finally a discussion on clinical management of DDIs will be done.

2.4.1 Concept of DDIs

The term drug-drug interactions can be defined as "*the pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone*" (Tatro, 2005). As described by Tatro (2005), the effect of a DDI may be one of the following:

- Antagonism, such as a loss of blood pressure control by clonidine when tricyclic antidepressants are added to a regimen.
- Synergism, as an example of which is the increased anticoagulant effect resulting from administering salicylates and warfarin.
- Idiosyncratic, such as the possible though rare severe effects that have been associated with patients concurrently receiving pethidine and monoamine oxidase inhibitor (Jankel & Fitterman, 1993:52).

DDIs are well-recognised causes of adverse drug effects (ADEs) (Bates *et al.*, 1995:29). According to Juurlink *et al.* (2003:1652), DDIs do cause particularly important type of adverse drug event because they are often predictable based on previous reports, clinical studies, and an understanding of pharmacological principles.

According to Johnson *et al.* (1999:193), DDIs are classified as an important category of ADEs. Drug interactions result in undesirable modification of the action of one or more concurrently administered agents. The interaction may cause treatment failure, an increased pharmacologic effect, or a toxic effect, which may be fatal. Because DDIs usually have a specific time course (i.e., onset and duration), they are more predictable (and preventable) then ADRs (adverse drug reactions). Bates *et al.* (1997:307) state that preventable DDIs account for about one third of ADEs but incur about one half of the total ADE costs.

In HIV-infected patients, the introduction of HAART has led to reduced morbidity and mortality in treated patients (Egger *et al.*, 2002:119). However, in a substantial proportion of patients, the effectiveness of HAART has not been sufficient due to occurrence of virological failure and immunological decay (Bartlett *et al.*, 2001:1369). All this has been due to failure to determine drug interactions and prevention of toxic effects (Boffito *et al.*, 2005a:375).

2.4.2 Types of DDIs

According to Seden *et al.* (2009:5), DDIs may arise due to the pharmacokinetics or pharmacodynamics of administered compounds. DDIs can be classified as pharmacokinetic or pharmacodynamic (Young, 2005:286; Cohen *et al.*, 2002:42) or pharmaceutical (Hall, 1986:192).

2.4.2.1 Pharmaceutical interactions

Pharmaceutical interactions occur when two drugs are given together, e.g., in an infusion, or when a drug reacts with the infusion solution. While it is necessary to be aware of this type of interaction, it is relatively uncommon (Hall, 1986:192).

2.4.2.2 Pharmacokinetic interactions

Pharmacokinetic interactions may be defined as those interactions in which the disposition of the first drug is altered by the second drug or precipitant drug. As a result, the effect of the first drug is either diminished or increased. Pharmacokinetic interactions are divided into those that affect (Swart & Harris, 2005:56; Young, 2005:42; Cohen *et al.*, 2002:42):

- **Drug absorption**: An example of this interaction is when didanosine containing an aluminium-magnesium antacid buffer, is administered with ciprofloxacin, the metallic ions in the buffer may chelate with ciprofloxacin, resulting in subtherapeutic blood levels of ciprofloxacin (Sahai *et al.*, 1993:292).
- **Drug binding**: This was illustrated by in vivo work which showed that methadone concentrations were decreased when administered with ritonavir, due to displacement of methadone from plasma binding sites (Piscitelli & Gallicano, 2001:984).
- **Drug metabolism:** An example of this kind of interaction is between PIs and NNRTIS that act as inhibitors or inducers of cytochrome P450 (CYP450). Ritonavir is the most potent CYP450 and therefore the most likely to interact with other drugs such as amiodarone, cisapride or pethidine. Likewise efavirenz induces the metabolism of indinavir and saquinavir by reducing their plasma concentrations (Piscitelli & Gallicano, 2001:984).
- **Excretion:** In this case, the NRTIs may have additive or synergistic adverse effects, so if for example stavudine is administered with zalcitabine or didanosine, because these drugs are eliminated primarily by the kidney peripheral neuropathy caused by stavudine (Lee & Henderson, 2001:587).
- **Transport system:** One case report demonstrated a 48% decrease in valproic acid concentration after a patient had been started on lopinavir/ritonavir-based regimen (Sheehan *et al.*, 2006:148). This

interaction was likely to be due to the ability of ritonavir to induce valproic acid metabolism via glucuronidation (Sheehan *et al.*, 2006:148).

The result of pharmacokinetic DDIs may be an increase or decrease in the concentration of the drug at the site of action. The mechanism most common is drug metabolism.

2.4.2.3 Drug metabolism interactions

Drugs are metabolised by two types of reactions: phase I reactions that involve oxidation, reduction or hydrolysis in which drugs are turned into more polar compounds and phase II reactions that involve coupling drugs with some other substance (e.g. glucuronic acid) to make (usually) inactive compounds (Cohen *et al.*, 2002:42). These reactions make drugs more easily excretable. Drug metabolism interactions can increase or decrease the amount of drug available by inhibition or induction of metabolism (Cohen *et al.*, 2002:43).

2.4.2.4 Enzyme induction

Enzyme induction frequently affects phase 1 oxidation, which requires the presence of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and the haem-containing protein cytochrome P450. Enzyme inducers like carbamazepine, phenytoin, phenobarbital, PIs and NNRTIs, increase the activity of the microsomal enzymes (cytochrome P450 isoenzyme), increasing the rate of metabolism and excretion (Liedtke *et al.*, 2004:482). One study reported that there was a decreased metabolism and subsequent toxicity of carbamazepine when concomitantly administered with ritonavir (Bates & Herman, 2006:1190; Young, 2005:294). A case study reported of a patient who was prescribed ritonavir with midazolam concomitantly, and developed extreme sedation and possibly respiratory depression due to the inhibition of midazolam metabolism (Schmitt *et al.*, 2009:1175).

2.4.2.5 Enzyme inhibition

Enzyme inhibitors inhibit the microsomal enzymes (cytochrome P450 isoenzymes), decreasing the rate of metabolism and excretion of other drugs that are metabolised by these same enzymes (Cohen *et al.*, 2002:43). Examples of these drugs are PIs and delavirdine presenting drug interactions with statins because they are metabolised by the same enzyme (Geletko & ZuWallack, 2001:607). These drugs begin to accumulate in the body and toxicity may develop within 2 to 3 days. The clinical significance of the enzyme inhibition interaction depends on the extent to which serum levels rise. Some drugs may have additive or synergistic adverse effects. For example, AZT may cause anaemia and neutropenia, so drugs causing bone marrow

suppression should be prescribed with caution if used concomitantly (Matheny *et al.*, 2001:778). Another example of this metabolism was the administration of simvastatin with saquinavir/ritonavir, the interaction leading to increased levels of simvastatin by more than 3000% (Fichenbaum *et al.*, 2002:569). This could put the patient at risk for adverse effects like myalgias, rhabdomyolysis, elevated creatinine phosphokinase and hepatic dysfunction (Dube *et al.*, 2003:614).

2.4.2.5.1 Cytochrome P450 isoenzymes

Cytochrome P450 is a large family of related isoenzymes of which about 30 have been identified. The most frequently involved in drug interactions are CYP3A4 and CYP2D6. There are many drugs that are metabolised by these cytochrome P450 isoenzymes including ARVs (Clarke *et al.*, 2008: HS-3). Drugs may be metabolised by more than one cytochrome isoenzyme. For example, the majority of PIs and NNRTIs and antidepressants are substrates for, and can inhibit or induce the CYP450 system and have the potential to cause clinical drug interactions including serotonin syndrome, a potential fatal complication (DeSilva *et al.*, 2001:1281; Tseng & Foisy, 1999:461). According to Swart and Harris (2005:56) it is of value to know which particular isoenzymes are responsible for the metabolism of a specific drug as this makes it possible to predict with which other drugs it may possibly interact.

2.4.2.6 Pharmacodynamic interactions

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action, without alterations in the concentrations of either drug (Young, 2005:286; Cohen *et al.*, 2002:42). Sometimes one drug competes directly with another for particular receptors, but often the reaction is more indirect and involves the interference with physiological mechanisms, making pharmacodynamic interactions more difficult to classify than pharmacokinetic interactions (DeVane as quoted by Delafuente, 2003:139). There are four basic subdivisions as quoted by Swart and Harris (2005:59):

- **Additive or synergistic interactions and combined toxicity**: For example, peripheral neuropathy caused by stavudine can be potentiated by zalcitabine or didanosine if co-administered together (Macher *et al.*, 2003:41).
- **Antagonistic or opposing interactions:** An example in this interaction is when delavirdine (600 mg twice daily), an irreversible inhibitor of CYP3A4 was administered with amprenavir (600 mg twice daily), there was a strong bidirectional interaction whereby amprenavir reduced delavirdine exposure by 30% to 50% and delavirdine increased amprenavir exposure by approximately four-fold (Young, 2005:288). Another example is when zidovudine and stavudine are administered together, there is an

antagonistic effect, because these NRTIs compete for cellular thymidine kinase, the enzyme that is needed for the monophosphorylation of both drugs to nucleotides (Havril *et al.*, 2000:321).

- **Interactions due to changes in drug transport mechanisms**: This interaction has been reported in HIV patients who are prescribed methadone for the treatment of pain or drug addiction. Methadone interacts with most PIs and NNRTIs through complex mechanisms including induction of the CYP450 system and glucoronyltransferase, changes in plasma protein binding and induction of P-glycoprotein (Gerber, 2000:S123). For example, studies showed that when methadone was administered with efavirenz or nevirapine, there was an unexpected decrease in methadone concentration results, which could potentially lead to opiate withdrawal symptoms (Clarke et *al.*, 2002:1143; Stevens *et al.*, 2003:650).
- **Interactions due to disturbances in fluid and electrolyte**: It has been demonstrated that PI administration may be associated with alterations in plasma lipids and insulin levels placing some PI-treated patients at increased risk for coronary heart disease (Clotet & Negredo, 2003:19). An example is the administration of PIs and the statins, whereas statins are being an important component of pharmacotherapy for PI-associated dislipidemia. All statins except pravastatin are metabolised by the CYP3A4 enzyme system, therefore concomitant use of these drugs with PIs produce drug interactions and statin-induced hepatotoxicity and myopathy (Young, 2005:294).

2.4.3 Mechanisms of DDIs

Drugs interact with one another through various mechanisms which include altered absorption, altered distribution, altered metabolism and altered elimination.

2.4.3.1 Altered absorption

Drug interactions can occur where one drug changes the absorption characteristics of another drug. The binding of one drug to another, causes changes in gastric pH, and changes in gastrointestinal motility and can cause these drug interactions (Cohen *et al.*, 2002:42). The classic example of one drug binding another drug is that of tetracycline and calcium and magnesium containing antacids. The cations of the antacid bind the antibiotic molecule to prevent its absorption potentially causing a treatment failure.

Another example is that of didanosine which contains an aluminium-magnesium antacid buffer. When administering didanosine with ciprofloxacin, the metallic ions in didanosine may chelate concomitantly with ciprofloxacin resulting in subtherapeutic levels of the antibiotic (Sahai *et al.*, 1993:292). It is therefore recommended that the two drugs be administered at different times. Absorption of many drugs, such as

delavirdine, atazanavir, aspirin, ciprofloxacin, and digoxin, can be significantly impaired by concurrent administration of antacids by a variety of mechanisms (Fulco *et al,* 2006:1974).

2.4.3.2 Gastrointestinal motility

A mechanism of DDIs that may go unrecognised is where one drug changes the gastrointestinal transit time. In doing so, the pharmacokinetics of not altering the transit time can be changed, leading to changes in the drug's pharmacological actions. Drugs with anticholinergic properties and opioids will slow gastrointestinal motility, while drugs, such as metoclopramide and laxatives will increase gastric emptying and gastric transit and generally increase the rate of absorption (Benet *et al.*, 1990).

2.4.3.3 Altered gastric pH

Drugs that change the normal pH of the stomach can affect absorption characteristics of other drugs. This is an essentially important point, considering the widespread use of proton pump inhibitors, although only a few clinically relevant interactions have been identified (e.g. ketoconazole) (Delafuente, 2003:137). The results of data in a study done by O'Connor-Semmes *et al.* (2001:126) suggested that the elderly may be more sensitive to the increase in gastric pH compared to younger adults. Of clinical importance is the fact that a small increase in serum concentration of a benzodiazepine like trizolam could have significant adverse effects in a very old patient, leading to confusion and falling (Moore & O'Keeffe, 1999:15).

Increasing the gastric pH will allow enhanced absorption of weak bases. Examples of weak bases are albuterol, allopurinol, diazepam, diphenhydramine, metoprolol and morphine. According to Piscitell and Gallicano (2001:984), when didanosine is administered with indinavir, changes in pH may significantly alter drug absorption of indinivarir because of an increase in pH due to the didanosine buffer. It is therefore recommended that didanosine and indinavir be administered at least one hour apart.

It has been reported by Fulco *et al.* (2006:1974) and Tran *et al.* (2001:207) that acid-suppressive therapy with histamine-2 (H_2) blockers, proton pump inhibitors or antacids can cause a decrease in the absorption of some PIs. This is due to changes in the pH of the gastrointestinal tract. PIs like atazanavir, fosamprenavir, tipranavir have been found to have significant interactions with acid-suppressive therapy that require intervention due to the potential for virological failure from inadequate ARV concentration (Fulco *et al.*, 2006:1975).

2.4.3.4 Altered distribution

The most common DDI affecting drug distribution is alteration in protein binding. This type of interaction occurs when there is competitive inhibition for protein binding sites. This allows for the unbound fraction of the drugs to be increased, and it is the free fraction that is responsible for pharmacological activity (Young, 2005:292). Most of the clinically significant interactions involve drugs that are highly protein bound and have a narrow therapeutic index. An example of this is when the cytidine analogue lamivudine inhibits phosphorylation of another cytidine analog, zalcitabine, resulting in high incidence of toxicities. Therefore such combinations should be avoided (Young, 2005:292).

An example of this DDI is warfarin and aspirin, where the aspirin will increase the unbound fraction of warfarin by displacing it from the protein. Small changes in the warfarin free fraction can allow the prothrombin time to become elevated and may put the patient at risk of bleeding. For example, when zidovudine and stavudine are co-administered, the two NRTIs do compete for cellular thymidine kinase, the enzyme that is responsible for the monophosphorylation of both drugs to nucleotides. The inhibitory effect impairs the efficacy of stavudine when combined with zidovudine (Havril *et al.*, 2000:321).

2.4.3.5 Altered metabolism

This mechanism occurs through the cytochrome P450 isoenzyme by inhibition and induction.

2.4.3.5.1 Cytochrome P450 isoenzyme

Most of the clinically important types of pharmacokinetic DDIs are those altering a drug's metabolism. Many elderly patients, but not all, have underlying impaired CYP450 metabolising capability. According to Flockhart and Tanus-Santos (2002:405), six CYP450 isoenzymes that have been identified to be involved in oxidative metabolism of most commonly used drugs are: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

More than 50% of drugs metabolised by the CYP450 system are metabolised by CYP3A4 (Michalets, 1998:84). For the elderly this is extremely important because hepatic CYP3A4 declines 8% per decade in older adults (Chapron, 2001:257). As stated by Michalets (1998:84) CYP2D6 is the next most common CYP450 isoenzyme involved, accounting for approximately 25% of the CYP450 drug metabolism. Genetic polymorphism of CYP450 enzymes occurs, leading to individuals who may have either poor or extensive

metabolising capabilities. Other factors, such as age, nutrition, hepatic contributions and hormones may affect CYP450 metabolism.

Interactions involving the CYP450 enzymes are often due to either inhibition of an isoenzyme, leading to increased blood or tissue concentrations of the substrate, or induction of an isoenzyme, causing enhanced metabolism and lower substrate concentrations (Delafuente, 2003:137). According to Johnson *et al.* (1999:193) enzyme inhibition is the mechanism most often responsible for life-threatening interactions. Such interactions have been observed when zalcitabine is combined with stavudine or didanosine producing severe peripheral neuropathy, pancreatitis, and lactic acidosis (Simpson & Tagliati, 1995:153).

Induction of certain CYP450 isoenzymes, for example CYP2C9/19 by lopinavir/ritonavir and nelfinavir was reported by Honda *et al.* (1999:302) and Lim *et al.* (2004:1034) that it could lead to an increase in the matabolism of antiepileptic drugs like phenytoin, a norrow therapeutic index drug. The reduction in the anticonvulsant serum concentration could lead to seizures.

2.4.3.5.2 Cytochrome P450 inhibition

Competitive binding at the enzyme's binding site between two drugs is often responsible for inhibition of a drug's metabolism. The onset of CYP450 inhibition depends on the inhibiting drug's half-life. For drugs with short half-lives, enzyme inhibition occurs quickly and clinically significant interactions can be apparent within 1 or 2 days (Cheng *et al.*, 2009:155). Inhibition of CYP450 is also dose-dependent. Higher doses of an inhibitory drug will cause greater amounts of competitive inhibition than lower doses. Although sufficient data are not available to help in clinical situations as stated by Delafuente (2003:137), knowing the CYP450 enzymes involved in a drug's metabolism can be used to predict and avoid clinical problems resulting from drug interactions.

All currently marketed PIs – atazanavir, amprenavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir (Young, 2005:287) – and the NNRTI delavirdine inhibit CYP3A4 (Piscitelli & Gallicano, 2001:984) decrease the hepatic clearance of CYP3A4 substrates and increase their plasma levels.

2.4.3.5.3 Cytochrome P450 induction

The onset of enzyme induction is usually longer than that of enzyme inhibition (Chapron, 2001:257). Enzyme induction is dependent on the half-life of the synthesis of new CYP450 isoenzymes and is dependent on the half-life of the inducing drug. Like inhibition of CYP450 enzymes, shorter half-life drugs will have a shorter

onset of induction. A drug with a long half-life, such as phenobarbital, may take one week before enzyme induction is seen. Drugs often involved in induction of CYP450 isoenzymes are carbamazepine, phenytoin, phenobarbital, primidone, and rifampicin (Clarke *et al.*, 2008: HS-5). Aging may impair enzyme induction, but this is not a universal finding as stated by Chapron (2001:257).

Of the ARVs, the NNRTIs nevirapine and efavirenz induce CYP3A4, thus increasing the hepatic clearance of CYP3A4 substrates and decreasing their plasma levels (Piscitelli & Gallicano, 2001:985). Other ARVs like PIs induce CYP450 isoenzymes, and it has been reported that drugs like phenytoin, rifampin, carbamazepine, phenobarbital, and dexamethasone can increase the hepatic clearance and therefore decrease plasma concentrations of the PIs (Lesho & Gey, 2003:675).

2.4.3.5.4 Altered renal elimination

Many drugs and drug metabolites are excreted in the urine via renal tubular secretion. Two drugs can compete for the same active secretion sites in the tubule allowing for decreased elimination and potentially toxic serum concentrations (Lesho & Gey, 2003:675). Aspirin and probenecid are good examples of drugs that can be involved with this type of DDI. Probenecid can decrease renal elimination of methotrexate and penicillin (Hansten, 1995). Alteration in urine pH can also affect drug elimination. Alkalinisation of the urine will decrease elimination of drugs that are weak bases and decreases in urine pH will increase their elimination. Acidification of the urine will decrease renal elimination of drugs that are weak acids (Hansten, 1995).

This mechanism happens in interactions that alter drug bioavailability by decreasing it and these are commonly found in PIs. The reason is that PIs induce CYP450 isoenzymes, so drugs like phenytoin, rifampin, carbamazepine, phenobarbitone, and dexamethasone can increase the hepatic clearance, thereby decreasing plasma concentrations of the PIs (Lesho & Gey, 2003:675). All this result in increase in toxicity of the drugs (Lesho & Gey, 2003:675). In the elderly as stated by Delafuente (2003:139), more common and potentially more significant are DDIs that affect renal function. Glomerular filtration rates decline with advanced aging. To compensate for this physiologic change, a compensatory production of vasodilatory renal prostaglandins occurs (Delafuente, 2001:499).

Nonsteroidal anti-inflammatory drugs can markedly impair this compensatory mechanism leading to decreased renal function. When this happens there is a decrease in elimination of renally eliminated drugs. Therefore, serum creatinine concentration must be monitored for rises after beginning a nonsteroidal anti-inflammatory drug and for drugs with narrow therapeutic ranges that are renally eliminated (e.g. digoxin)

serum concentrations may need to be determined when nonsteroidal anti-inflammatory drugs are prescribed on a chronic basis (Delafuente, 2003:139). However, according to Swedko *et al.* (2003:356) in frail elderly patients, serum creatinine concentrations may be very misleading, often in the normal range despite poor renal function.

2.5 DYNAMICS OF DDIs

It is necessary to determine the circumstances in which drugs might interact, and when the clinical situation would be protective or aversive, by adding or subtracting Drug A to or from Drug B, and vice versa (Strain *et al.*, 2004:88). For example, if Drug A and Drug B were started simultaneously and Drug A had the potential to alter the metabolism of Drug B, regularly monitoring the clinical response may be protective in that the net effect of the interaction could be adjusted as the clinician treat the patient either until improvement or toxicity.

Adding Drug A to Drug B where Drug A alters the metabolism of Drug B, might change (increase/decrease) the concentration of B, which is already in the patient's system, and initiate an adverse drug response. Before adding Drug A, Drug B might have been at a stable therapeutic dose. Three situations might prevail: higher concentration of B, less of B, or thirdly, a pharmacologic or pharmacodynamic interaction with additive incidence or severity of an adverse event. On the other hand, adding Drug B to a steady state of Drug A, where Drug A alters the metabolism of Drug B but Drug A is not affected by Drug B, will not be aversive, as the clinician may add more or less of Drug B, depending upon the clinical situation. Thus the clinician can compensate for the interaction by adjusting the dose of Drug B. An approach to observing DDIs is to outline Drug A's impact on Drug B when adding and subtracting one drug to and from the other (see Table 2.21)

Table 2.21: Drug interactions: adding drugs

Patient is on		**Add on**	
A	Drug A alters metabolism of drug B	**B**	No impact as the effects of A on B will be accounted for as B is initiated
A and B	Drug A alters metabolism of drug B		No action is necessary if there are no adverse effects present, the patient is stable on both and the interaction is accounted for
B	Drug A alters the metabolism of drug B	**A**	Dose of B may need to be adjusted as the effect of A and B is observed

Removing Drug A from Drug B or Drug B from Drug A, where Drug A alters metabolism of Drug B, presents additional issues: Discontinuing one drug may raise or lower the concentration of another, may alter the clinical effects of the remaining drug and/or may precipitate toxicity. The practitioner needs to assess the clinical effects of the remaining drug during withdrawal of the second drug (see Table 2.22).

Table 2.22: Drug interactions: removing drugs

Patient on		Take away	
A and B	Drug alters metabolism of drug B	**B**	No change in the dose of A will be necessary
A and B	Drug alters metabolism of drug B	**A**	The dose of B may need to be altered as the effect of A on B dissipates

2.6 DDIs RATING SYSTEM: SIGNIFICANCE LEVELS

Most rating systems as employed by Tatro (2005) and reported by De Maat *et al.* (2004:122) indicate

- major significance,
- moderate significance; and
- minor significance.

2.6.1 Major significance: level 1

Significance level 1 indicates a major contradiction or a drug interaction that requires very careful monitoring. According to Strain *et al.* (2002b:284) the effects are potentially life-threatening or capable of causing permanent damage. The clinician needs to document why he or she is prescribing this combination, and the medical necessity to use both drugs concomitantly only if there is no alternative or the potential benefit outweighs the risk. Drug combinations producing an interaction with a significance level 1 are combinations that result in serious and potentially life-threatening adverse effects such as arrhythmia, respiratory depression and/or death (Winston & Boffito, 2005:4).

Obviously, if this combination is to be used the drug(s) in question must be prescribed with an explanation as to the need for their concomitant use and must be preceded by very cautious monitoring. Documentation of the clinician's awareness of the potential serious – level 1 – interaction should be accomplished at the time of prescribing this potentially dangerous combination. In addition, it is obligatory to alert the other health care providers' of the potential interactions and adverse outcomes which they could expect. Obviously, the

optimum choice, if possible, is to use an alternative medication to avoid significance level 1 interactions (Strain *et al.*, 2004:89).

2.6.2 Moderate significance: level 2

With significance level 2, the effects may cause deterioration in a patient's status. Additional treatment, hospitalisation or extension of hospital stay may be necessary (Strain *et al.*, 2002b:284). The potential interaction must also be documented and the clinical outcome(s) must be monitored carefully so that unacceptable, pernicious reactions are halted as soon as possible.

According to Strain *et al.* (2004:89) it is essential that the clinician document that the potential drug interactions were considered when using this combination. It is also essential to alert the patient's health care providers to the potential interactions so that they are observed early in their course.

2.6.3 Minor significance: level 3

As stated by Strain *et al.* (2002b:284) the effects are usually mild. Consequences may be bothersome or unnoticeable, but should not significantly affect the therapeutic outcome. Additional treatment is usually not required (Tatro, 2005). According to Strain *et al.* (2004:89) significance level 3 does not preclude the use of a specific drug, but clinical decision making requires acknowledging if the adverse reactions (e.g. nausea and rash) might be precluded by choosing an alternative drug. The potential interaction and its mechanism(s) needs documentation in the patient's medical chart and the patient's health care providers need to be informed.

Another rating system is employed by *Drug Interaction Facts* which utilises a 5 point significance classification scheme (Tatro, 2005) and *Facts and Comparisons* (McEvoy, 2000) and they recommended the following:

- Avoid combination: risk always outweighs benefit.
- Usually avoid combination: use combination only under special circumstances.
- Minimise risk: take action as necessary to reduce risk.
- No action needed: risk of adverse outcomes appears small.
- No interaction: evidence suggests no interaction.

2.7 POSSIBLE CAUSES OF DDIs

2.7.1 Drug combinations

Drug combinations of interacting drugs are among the major causes leading to DDIs (Seden *et al.*, 2009:5). Drug combinations are more common in an elderly population using many drugs (Bjőrkman *et al.* 2002:1680). A large proportion of these combinations are likely to be part of a normal drug regimen. In a study done by Bjőrkman *et al.* (2002:1676), in DDIs most of the drug combinations increased the risk of ADRs and lowered therapeutic effects as stated by Seymour and Routledge (1998:485). In all potential DDIs, 50% of the combinations could result in an adverse drug reaction and 50% in a suboptimal therapeutic effect. However, combination ARV treatment is a potent and effective therapy for HIV infection (Pontali, 2007:26). This is also a disadvantage because ARV drugs frequently interact amongst themselves and other drugs. Since some of these drug combinations have negative effects, more attention must be focused on detecting and monitoring patients using such combinations and could also be addressed by dose adjustment.

2.7.2 Lack of communication and medication history

Communication between emergency departments and primary care physicians often does not occur (Beers *et al.*, 1990:61), and primary care physicians do not take down medication histories optimally and therefore, the physicians responsible for follow-up may be unaware of the changes made in therapy.

Emergency department physicians do not routinely screen for potential drug interactions due to unavailability of a medication history. In a study by Beers *et al.* (1990:63) it was stated that groups of patients at higher risk of drug complications, the elderly and those taking multiple medications, did not appear to receive more cautious care. Neither the physician's record nor the instructions given to the patient indicated that prescribing physicians recognised the potential adverse reactions that were introduced. There is need for physians to screen for interactions. A patient's advanced age or a long list of medications should cause the physicians to be more reticent in prescribing. Fewer medications should be given to the elderly and to high medication users.

2.7.3 Increase in number of newly marketed drugs

There is a considerable number of newly marketed drugs with a growing number of possible combinations. Complex disease states often require the concurrent use of these drug combination therapies so as to be highly effective (Bergk *et al.*, 2004a:595). Nevertheless, as supported by Merlo *et al.* (2001:427) multiple

drug use is also associated with the occurrence of DDIs. Therefore the majority of these interactions can be compensated by dose adjustment or prevented by a well-considered sequence of administration (Bergk *et al.*, 2004b:86). The considerable number of newly marketed drugs with a number of possible combinations raises the need to support general practitioners with the pertinent information for careful approach to patients.

2.7.4 Polypharmacy

Polypharmacy, the use of two or more medications by one patient, has become prevalent especially in elderly patients (Gaeta *et al.*, 2002:159). Beers *et al.* (1989:105) in their study showed that those 65 years of age and older used an average of two to six prescribed medications and one to four non-prescribed medications per day. The frequency of polypharmacy in the elderly increases the incidence of adverse drug reactions and interactions, and it is the most significant contributing factor for DDIs. Patient's past medical history and medication has to be evaluated by the physicians. According to Seden *et al.* (2009:5), polypharmacy is largely unavoidable for patients receiving ARVs in both the developed and developing world and resource-poor setting, with life-long treatment and change of drug combinations along the way.

2.8 PATIENTS AT RISK FOR DDIs

Patients that are at risk for DDIs are discussed in this section with specific reference to the elderly and the HIV/AIDS patients.

2.8.1 The elderly

The incidence of adverse drug reactions and interactions in the elderly has been reported to be two to three times the incidence in younger patients (Nolan & O'Malley, 1998:105). According to Sloan (1992:2709), this increased risk for the elderly may be related to impaired organ reserve capacity, multiorgan dysfunction, and altered pharmacokinetics and pharmacodynamics.

2.8.2 People living with HIV/AIDS

The HIV infection is treated by using HAART, which involves a regimen of at least three agents to be effective (Seden *et al.*, 2009:5). In a study on DDIs in general medical patients, Sanderson (2005:22) found that the risk of DDIs rose from 13% in patients taking two drugs to 82% in patients taking seven drugs or more.

2.9 PREVALENCE OF DDIs

Drug-drug interactions are widely unrecognised in clinical practice as the source of medication errors, responsible for increased morbidity in patients and this result in significant opportunity cost for the health care systems (Seden, 2009:5). DDIs are of great concern to the health care providers for they are known to be related to adverse drug reactions and hospitalisations (Kristina & Inga, 2007:911). DDIs are the result of drugs interacting with other drugs by altering their absorption, distribution, metabolism, or excretion (pharmacokinetic interactions) or through pharmacodynamic interactions in which they can interact by modifying the pharmacologic actions of other drugs through additive, synergistic, or antagonistic effects (Young, 2005:286 ; Cohen *et al.*, 2002:42).

Little information is available on the epidemiology of DDIs in clinical practice, and most of the evidence is derived from case reports, volunteer studies, or investigations of potential DDIs in hospitalised patients (Halkin *et al.*, 2001:260). Retrospective prescription audits of community-based practices showed prevalence rates of potential drug interactions in the range of 4% to 6%. These rates increased with the number of drugs prescribed, the number of prescribing physicians per patient, as well as with patient age (Seymour & Routledge, 1998:485). According to Leape *et al.* (1995:35), in a systemic analysis of adverse drug events, DDIs accounted for 3% to 5% of all in-hospital medication errors.

Although only an estimated 10% to 15% of potential interactions are clinically significant, according to Hamilton (1998:1112) these could have been serious enough to account for approximately 3% of medical admissions. DDIs have been shown to cause a decline in functional abilities especially in older people (Delafeunte, 2003:134). Drugs can interact to alter the absorption, distribution, metabolism, or excretion of a drug and interact in a synergistic or antagonist fashion thus altering their pharmacodynamics (Young, 2005:286). Although adverse drug reactions caused by drug interactions were recognised as a major health problem (Juurlink *et al.*, 2003:1652), there are also DDIs that lead to treatment failure without causing any instant and clinically visible harm to the patient.

The incidence of potential DDIs increase with increased drug use and such interactions are responsible for numerous emergency room and physician visits and hospital admissions. Rastegar *et al.* (2006:933) confirmed that the co-administration of contraindicated drugs was found to account for 5.2% of 209 hospital admissions. Another study by De Maat *et al.* (2004:121) confirmed an incidence of 23% to 26% of clinically significant DDIs of 220 HIV-infected outpatients in the Netherlands.

2.9.1 Emergency departments

Recent data on the incidence of potential DDIs in community-dwelling elderly is difficult to find. Data are available from several studies conducted in emergency departments. Goldberg *et al.* (1996:447) retrospectively reviewed medical records of patients seen in two emergency departments and results revealed that 47% of the patients had potential DDIs. The incidence of potential DDIs increased as the number of total medications increased, ranging from 13% for two drugs to 82% for seven or more medications. In more than 50% of the patients, the drug interactions were responsible for the emergency department visit (Goldberg *et al.*, 1996:448).

2.9.2 Ambulatory settings

Hanlon *et al.* (2002:166) conducted an epidemiological study of elderly ambulatory patients and identified a 13.2% incidence of potential drug-drug or drug-disease interactions and 11.2% of patients had a potential duplication in dose or were receiving a drug for inappropriately long duration. The study emphasised that vigilance must continuously be used to identify the potential for DDIs and patients should be closely monitored to ensure that no clinically significant problems arise.

2.10 DRUG-DRUG AND DRUG-DISEASE INTERACTIONS

The potential for drugs to interact adversely with a variety of diseases (drug-disease interactions) has only been addressed rarely (Adams *et al.*, 1987:39). According to Herr *et al.* (1992:1331) in was observed that patients in a certain population group appeared to have substantial risk for drug-drug (47%) and drug-disease (22%) interactions. Approximately half of potential drug-drug and one third of potential drug-disease interactions are attributable to medications administered or prescribed in emergency departments (ED). In their high-risk population, the potential for an adverse drug interaction (ADI) increased from 13% to 81% as the number of medications increased from two to seven or more (Goldberg *et al.*, 1996:449).

Drug interaction issues continue to present a major dilemma for the clinician caring for complex patients such as those infected with HIV (Krikorian, 2005:278). These patients are treated by using HAART that has contributed to improved quality of life and longer life expectancy (Stanic & Grana, 2009:47). Clinically significant DDIs involving ARVs in HAART are common, and have been reported by Shah *et al.* (2007:277) to affect at least 14% of 342 patients in the USA, and 23% to 26% 0f 220 HIV-infected outpatients in Netherlands according to De Maat *et al.* (2004:121).

2.10.1 Drug-disease interactions

Certain drugs have the capacity to exacerbate acute and/or chronic disorders (May, 1997; Tatro, 1996). Beta-adrenergic blocking agents, anticonvulsants, can precipitate and exacerbate disease such as asthma, chronic obstructive pulmonary disease, epilepsy, peripheral vascular disease and HIV/AIDS (Cohen *et al.*, 2002:45). These drugs can also blunt the typical signs and symptoms of a hypoglycaemic reaction in diabetic patients and alter insulin utilisation in the body.

Beta-adrenergic blocking drugs and calcium channel modulators, particularly verapamil, have negative inotropic and negative chronotropic effects on the heart and can exacerbate diseases such as congestive heart failure (Brown, 2004). Prednisone can aggravate congestive heart failure and can cause fluid overload (Brown, 2004). Because a number of these interactions may have an insidious onset, continuous long-term monitoring of patients may be needed.

2.10.2 Diseases at high-risk for adverse drug interactions

Patients with congestive heart failure, hypertension, diabetes, and renal disease are at high relative risk for ADI (Goldberg *et al.*, 1996: 449). These results corroborated by data from Adam *et al.* (1987: 39) whose study found that patients with renal or heart failure, and hypertension were at highest risk of drug-disease interactions.

2.10.3 Drugs that are responsible for the majority of potential ADIs

A relatively small number of medications are responsible for the majority of potential ADIs (Goldberg *et al.*, 1996:449). These findings were supported by Beers *et al.* (1990:61) who found that 89% of ADIs were attributable to five drug classes: Narcotic, analgesic, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, antacids, and diuretics. Karas (1981:627) found 90% of potential ADIs from ten drugs: aspirin, steroids, digoxin, propranolol, phenytoin, aminophylline, prochlorperazine, quinidine, penicillin, and acetaminophen with chlorzoxazone.

Likewise, Herr *et al.* (1992:1331) reported that 90% of ADIs were associated with antihypertensives, digoxin, theophylline and carbamazepine. One study reported an increase in carbamazepine concentrations increasing from 9.5 mcg/ml to 17.8 mcg/ml within 12 hours of a single dose of ritonavir 200 mg (Kato *et al.*, 2000:851). Therefore to patients receiving both drugs careful monitoring of carbamazepine levels is essential.

In summary, patients taking three or more medications or patients older than the age of 50 years taking two or more medications are at substantial risk for adverse drug-drug and drug-disease interactions (Kristina & Inga, 2007:911). Particular medications, as well as clinical entities such as hypertension, congestive heart failure, diabetes, and renal failure, are associated with higher relative risks of interactions (Herr *et al.*, 1992:1331). Therefore, the routine of screening of elderly patients fitting high-risk profiles should be considered.

Studies done reported that persons with acquired immunodeficiency syndrome (AIDS) received on average 5.6 prescription medications throughout their disease course, and this number may be as high as 9 (Greenblatt *et al.*, 1991:136 ; Harb *et al.*, 1993:919). With the development and testing of new ARVs and drugs for opportunistic infections associated with HIV disease, the issue of polypharmacy and multiple drug interactions became increasingly complex (Acosta & Fletcher, 1995:73; Seden *et al.*, 2009:5; Stanic & Grana, 2009:47). Since ART and treatment or prophylaxis of opportunistic infections is lifelong, the nature of these interactions requires delineation to provide an optimal pharmacologic strategy for the use of these agents in combination.

According to Greenblatt *et al.* (2000:335), pharmacokinetic interactions involving ART may critically influence the efficacy and toxicity of these drugs, as well as pharmacologic treatments of coincident or complicating diseases. The viral PI ritonavir is of particular concern since it both inhibits and induces the activity of cytochrome P450 3A (CYP3A) isoforms (Mathias *et al.*, 2008:64).

Significant drug interactions exist at major processes governing the pharmacokinetic disposition of available ARV agents: absorption of ARV compounds can be inhibited (i.e. didanosine with food) (Shyu *et al.*, 1991:503); metabolism can be inhibited (i.e. zidovudine plus fluconazole) (Lavrijsen *et al.*, 1990:402) or induced (i.e. zidovudine plus rifampicin) (Burger *et al.*, 1993: 1426); and renal excretion can be decreased (i.e. zidovudine plus probenecid) (De Miranda *et al.*, 1989:494).

Most HIV-infected persons will require numerous medications ranging from two to seven or more, as their disease progresses, and as long as therapy is continued, the potential for drug interactions is present and will require continuous monitoring (Sanderson, 2005:22). Because therapeutic choices are not unlimited, some interactions will occur (Acosta & Fletcher, 1995:80). Therefore researchers and clinicians are faced with the audacious task of understanding and anticipating these interactions and, applying their clinical findings in order to provide optimal therapy for patients infected with HIV.

2.11 PHARMACOLOGICAL ASPECTS OF DDIs BETWEEN ARVs

DDIs are a serious complication of taking multiple medications and account for 3% to 5% of all hospital medication errors (Leape *et al.,* 1995:36). According to Clarke *et al.* (2008: HS-3), the consequences of drug interactions vary ranging from drug toxicities to therapeutic failures, or loss of effectiveness and can significantly affect a patient's clinical outcome. Of particular concern are drug interactions in patients infected with HIV who are receiving HAART because it involves a regimen of a least three agents (Seden *et al.*, 2009:5).

HAART has revolutionised the management of HIV-1 infection and the ARV therapy has improved steadily in terms of efficacy, tolerability, and dosing convenience since the advent of HAART in 1995 (Chandwani & Shuter, 2008:1023). HAART consists of four classes that are available for ARV therapy: (Nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs; non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); and a fusion inhibitor). The strongly recommended regimen based on the existing efficacy data, is either NNRTI-based or PI-based HAART (Yeni *at al.*, 2004:252).

2.11.1 Clinically significant drug interactions associated with HAART

One of the most challenging issues faced by health care providers treating patients with HIV-1 infection is the complex problem of DDIs associated with HAART (Seden *et al.*, 2009:5; Stanic & Grana, 2009:47; Clarke *et al.*, 2008:HS-3; Pontali, 2007:26; Krikorian, 2005:278 ; Cohen *et al.*, 2002:42). The guidelines for the initial treatment of HIV infection recommend the use of at least three ARVs (Bartlett *et al.,* 2006a:2051), each of which is associated with significant drug interactions (DHHS, 2003). Drug interactions associated with HIV medications can be classified into those that alter the pharmacokinetics and those that alter pharmacodynamics (Seden *et al.*, 2009:5).

Pharmacokinetic drug interactions result in a change in pharmacokinetic parameters, such as the area under the curve (AUC), which measures drug exposure, peak concentration (Cmax), through concentration or half-life (Young, 2005:286; Cohen, 2002:42). Pharmacodynamic interactions result in alterations in the pharmacologic activity of the medication; not causing a change in the pharmacokinetic (Young, 2005:286; Cohen, 2002:42). The most common drug interactions in HIV medicine are pharmacokinetic interactions as a result of a change in the absorption, distribution and metabolism and the result of the concurrently administered medication (Piscitelli & Gallicano, 2001:984).

2.11.2 Influence of cytochrome P450 (CYP450) on DDIs in HIV

The cytochrome P450 enzyme system is responsible for the biotransformation of drugs from active to inactive metabolites that are readily excreted by the body. DDIs are more common in PIs and NNRTIs (Seden *et al.*, 2009:1; Winston & Boffito, 2005:1; Young, 2005:288; Cohen *et al.*, 2002:43). Of the numerous isoenzymes of CYP450 that have been identified, the ones responsible for elimination of drugs used in HAART are CYP3A, CYP1A2, and CYP2D2 (Clarke *et al.*, 2008: HS-3).

2.11.3 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs & NtRTIs)

The NRTIs are valuable ARV agents in the treatment of HIV infection because they constitute the "backbone" of highly active ARV therapy regimens (Waters & Boffito, 2007:213). Drug interactions associated with NRTIs and NtRTIs are few because these drugs are not metabolised by the CYP450 system (Clarke *et al.*, 2008: HS-3). However, drug interactions may still occur within these drugs. One of the few pharmacodynamic interactions encountered in HIV medicine occurs, for example with co-administered zidovudine and stavudine, since both drugs are thymidine analogues and they can compete for the same phosphorylation site in the growing chain of HIV DNA, resulting in an antagonistic, pharmacodynamic interaction (Piscitelli & Gallicano, 2001:986). It is therefore recommended that these two drugs never to be combined.

The use of didanosine (ddI) is complicated by drug interactions (Cohen *et al*, 2002:42). It is a buffered tablet form containing magnesium and calcium to improve systemic absorption. It, however, interacts with certain antibiotics like ciprofloxacin, tetracycline and therefore, to minimise the interaction, didanosine should be administered at least two hours after or six hours before the fluoroquinolone (Knupp & Barbhaiya, 1999:66). Concurrent use of didanosine-buffered tablets may also impair the absorption of the PI atazanavir, since atazanavir requires an acidic environment for absorption. To minimise the interaction, patients should take a didanosine-buffered tablet two hours after or one hour before taking atazanavir.

The most significant didanosine drug interaction reported occurs when didanosine is used concurrently with the NrRTI tenofovir. The didanosine AUC increases by 60% and therefore it is recommended that in patients receiving these two drugs concurrently and weighing > 60 kg, the didanosine dosage should be reduced from 400 mg to 250 mg once daily or from 250 mg to 200 mg in patients who weigh less than 60 kg (Young, 2005:292). For severely underweight patients, the dose should be further reduced to 125mg once daily (Faragon & Piliero, 2004). All patients receiving concurrent tenofovir and didanosine should be closely

monitored for didanosine -related toxicities such as pancreatitis, hyperlactatemia, and lactic acidosis, regardless of didanosine dosage adjustments.

2.11.4 Non-Nucleoside Reverse Transciptase Inhibitors (NNRTIs)

Drugs in this group are prone to drug interactions because they are extensively metabolised via CYP3A4 and can act as either inducers or inhibitors of CYP3A4. Nevirapine and efavirenz are inducers of CYP3A4, while delavirdine is an inhibitor of CYP3A4 (Pfister *et al.*, 2003:130). Therefore, when one of these drugs is combined with a drug that is also metabolised by CYP3A4, a drug interaction may occur (Clarke *et al.*, 2008: HS-3).

Nevirapine presents with numerous drug interactions, being a CYP3A4 inducer, and drug interactions associated with it lead to an increase in metabolism and reduced concentration of the co-administered drug. For example, when nevirapine is concurrently given with methadone, withdrawal symptoms may occur as a result of reduced methadone levels (Pinzanni *et al.*, 2000:496). Efavirenz is a potent inducer of CYP3A4 in vivo. Like the PIs, EFV is extensively metabolised primarily by the CYP3A4 (Pfister *et al.*, 2003:130).

The induction properties of efavirenz can result in reduced concentrations of concurrently administered drugs that are metabolised by CYP3A4 and it is therefore contraindicated with midazolam, triazolam and ergotamine derivative since there is a potential for increased drug concentrations of these medications and associated toxicity. Efavirenz, as a potent inducer of CYP3A4 is suggested to have a potential interaction with lopinavir and ritonavir, both of which inhibit CYP3A4. This interaction was assessed in a parallel group study in which PI-experienced, NNRTI-naive; HIV-infected patients received different doses of these agents (Young, 2005:286).

2.11.5 Non-Nucleoside Reverse Transcriptase and Protease Inhibitors Interactions (PIs)

When predicting potential drug interactions, it is important to know which P450 isoenzyme is responsible for the metabolism of a drug. Drug interactions between NNRTIs and PIs are common, as all currently available agents in these two classes are metabolised mainly by the 3A4 isoenzyme of the CYP450 system (Fichtenbaum & Gerber, 2002:1196). NNRTIs and PIs also inhibit or induce CYP3A4, decreasing or increasing hepatic clearance and, thereby, increasing or decreasing plasma levels, respectively, of drugs metabolised by CYP3A4. Therefore, depending primarily on the potency of each NNRTI or PI as an inhibitor or inducer of CYP3A4 and on the substrate affected, each one has a different drug interaction profile.

All currently marketed PIs – atazanavir, amprenavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir – and the NNRTI delavirdine inhibit CYP3A4 (Piscitelli & Gallicano, 2001:986). According to Von Moltke *et al.* (1998:107), ritonavir is the most potent CYP3A4 inhibitor and, consequently, has the most drug interactions, while amprenavir, indinavir, lopinavir, and nelfinavir appear to inhibit CYP3A4 equally, and saquinavir with the lowest inhibitory effect.

2.11.6 Effect of PIs on Nucleoside Analogues

The nucleoside analogue reverse transcriptase inhibitor, tenofovir, does not appear to inhibit CYP3A4 isoenzyme significantly and, like most inhibitors, is excreted by the kidneys. Tenofovir is associated with several drug interactions, particularly a bidirectional effect (i.e. agent can alter plasma levels of the other) with atazanavir, while atazanavir raises plasma levels of tenofovir (Holder, 2003).

Indinavir does not alter the pharmacokinetics of zidovudine, stavudine or lamivudine (Gulick *et al.*, 1997:735). This is because the optimal absorption of indinavir requires a normal (acidic) gastric pH whereas an acid medium rapidly degrades didanosine, which is formulated with buffering agents to increase the pH. Therefore the administration of indinavir and didanosine should be separated by at least 1 hour to avoid an interaction mediated by altered drug absorption (Gulick *et al.*, 1997:735)

2.11.7 Effect of NNRTIs on Nucleoside Analogues

Nevirapine is a potent and selective non-competitive inhibitor of reverse transcriptase (De Maat *et al.*, 2003:223). It does not compete with template or nucleoside triphosphates, and therefore a significant interaction would not be expected. Nevirapine may reduce plasma zidovudine concentrations by 25% but does not influence plasma concentrations of didanosine or zalcitabine (Murphy & Montaner, 1996:164).

NRTIs, unlike NNRTIs and PIs, are not metabolised by the hepatic CYP3A4 ezyme system and – the exception of zidovudine and abacavir - undergo renal rather than biliary excretion. Zidovudine undergoes hepatic glucuronidation and abacavir is metabolised in the liver by alcohol dehydrogenase (Barry *et al.*, 1999:390) Therefore, there is little potential for interaction between NRTIs and NNRTIs or between NRTIs and PIs. In addition, the NRTI class as a whole has fewer drug interactions than the NNRTI and PI classes have.

2.11.8 PIs interactions

The PIs are extensively metabolised by the cytochrome P450 (CYP) enzymes present in the liver and small intestine (Winston & Boffito, 2005:1). Therefore drug interactions involving PIs will occur largely as a result of enzyme induction or enzyme inhibition (Barry *et al.*, 1999:296). Some PIs can alter metabolism and thus the plasma concentration of other PIs, creating complex drug interactions when a second PI is added to HAART. According to Van Heeswijk *et al.* (2001:201), additionally, favourably positive DDIs can increase the exposure to PIs, allowing the use of lower doses at reduced dosing frequencies with fewer dietary restrictions.

Protease inhibitors have differing affinities for the CYP3A4 isoenzyme. The most potent inhibitor of CYP3A4 is ritonavir (Cooper *et al.*, 2003:1585), whereas the least potent is saquinavir. CYP3A4 inhibition associated with indinavir, nelfinavir, and amprenavir, and atazanavir tends to be intermediate. Ritonavir is often the most likely medication in the PI class to cause drug interactions because in addition to its CYP3A4 inhibition, it also inhibits CYP2D6 and induces CYP1A2 and CYP2C9 (Clarke *et al.*, 2009: HS-3). However, ritonavir is often used to enhance the pharmacokinetic parameters of co-administered PIs like indinavir (Kappelhoff *et al.*, 2005:276), due to its potent inhibition of their metabolism by CYP3A4 (Zeldin & Petruschke, 2004:5).

The use of boosted double PI regimen is presented with complex unexpected pharmacokinetic interactions (Winston & Boffito, 2005:2). Therefore combinations like tipranavir/ritonavir with others must be avoided because such combinations have shown to significantly reduce plasma concentrations of saquinavir, amprenavir and lopinavir (Boffito *et al.*, 2005b:1). Another interesting interaction that was observed by Boffito *et al.* (2004:1291) was with the boosted double combinations of atazanavir/saquinavir/ritonavir. Saquinavir levels are enhanced in this regimen further than when dosed with ritonavir alone, thus suggesting a role for this as a once daily regimen.

2.12 RISK FACTORS FOR DDIs WITH ARV AGENTS

According to Miller *et al.* (2007:1379) the risk factors for clinically significant drug interactions with ARVs remain poorly depicted. Drug interactions involving the NNRTIs and PIs are commonly caused by the significant effects on major metabolic pathways, including cytochrome P450 (CYP) 3A4 (Gerber *et al.*, 2005:308). Furthermore, there are numerous other known and unknown mechanisms responsible for a drug interaction in ARVs.

Miller *et al.* (2007:1383) in a retrospective medical review in an academic setting, using a logistic regression, identified specific risk factors that were independently associated with clinically significant drug interactions. These were age older than 42 years, more than three co-morbid conditions, treatment with more than three ARVs (excluding ritonavir used as a boosting agent), and treatment with a PI. Some of these factors are associated with more complex medical histories and advanced HIV disease. For example, the guidelines for the use of ARV agents in HIV-1-infected adults and adolescents recommend HAART regimens containing three active ARV agents for the treatment of naïve patients (National Department of Health, 2004:7).

Metabolic abnormalities in HIV epidemic can be considered among other risk factors. Fichtenbaum (2009:85) stated in his study that complications associated with HIV infection and ARV therapy include cardiovascular disease, lipid disorders, adipose tissue disorders, bone metabolism disorders, and lactic acidosis. These disorders have led to the discovery of new ARV regimens, and guidelines have had to change. Substantial complexity exists in the treatment, for example, of lipid disorders, resulting in complex DDIs between lipid-lowering agents and ARVs.

Another major risk factor for drug interactions is co-infection. In many developing countries, HIV/AIDS epidemiology may overlap with other infections such as tuberculosis (TB) disease (Seden *et al.*, 2009:6). It has been reported by WHO (2008b) that in some African countries up to 70% of new TB cases are detected in HIV-infected individuals. According to Naomi and Lee (2004:337), HIV infection is the most powerful known risk factor for progression from latent infection with *Mycobacterium tuberculosis* to active TB. TB-infected persons with HIV-associated immunosuppression progress to TB disease at a rate of up to 10% per year and treatment is further complicated by toxicity, malabsorption, DDIs and immune reconstitution paradoxical reactions. TB therapy, like HIV treatment, is complicated by drug resistance thus requiring multiple agents which have varying potential to interact with ARVs (Seden *et al.*, 2009:6; Winston & Boffito, 2005:2).

Other co-infections may include hepatitis C virus (HCV), a common cause of morbidity in HIV patients. According to Seden *et al.* (2009:6), emerging HCV therapies join ARVs in being among the most therapeutically risky drugs for DDIs, due to inhibition or induction of liver enzymes. Kempf *et al.* (2007:164) reported preliminary data for two HCV PIs in advanced development, telaprevir and boceprevir, suggesting that DDIs are likely to be the major issue in this class of drugs like in HIV PIs.

Opportunistic fungal infections that require treatment with azoles may have complex interactions with ARVs (Seden *et al.*, 2009:6). The exposure of many azole antifungals is increased by PIs and decreased by NNRTIs,

for example ketoconazole inhibit CYP450 metabolism and P-glycoprotein function, and therefore results in an increase in PI plasma exposure (Winston & Boffito, 2005:1).

An introduction of new ARV agents increases the number of effective regimens available, but also the complexity of treatment. Assessment of the potential for DDIs during the clinical phase of the drug development, although comprehensively undertaken, is at best incomplete. There are also surprises from unanticipated DDIs that emerge after the licensing, and may lead to increased risk of toxicity or diminished therapeutic index (Seden *et al.*, 2009:2). All this highlights the need for standard protocols for interaction screening of new drugs, as well as clinical vigilance as experience in their use develops.

Polypharmacy and an ageing population are important risk factors for HIV DDIs. As is expected the elderly are likely to be prescribed contraindicated medications alongside ARV regimens (DeLorenze *et al.*, 2005:63). An increasing number of patients over the age of 50 years living with HIV have been reported by Nguyen and Holodniy (2008:453), hence HIV will have to be managed alongside chronic conditions associated with ageing. As a result of disease state and metabolic side-effects of ARV regimens, HIV patients are often at high risk for cardiovascular disease, therefore the choice of their drugs like antihypertensives and lipid-lowering agents have to be carefully considered (Filardi *et al.*, 2008:238). It has also been established by Dhalla *et al.* (2006:242) that HIV infected patients get over-the-counter products that could interact with the prescribed ARVs. In Canada, for example, 19% of 632 patients taking ARVs and 61% of 293 HIV patients surveyed in the UK have used herbal remedies or supplements (Ladenheim *et al.*, 2008:653).

2.13 ROLE OF PHARMACISTS IN PREVENTING DDIs IN CLINICAL PRACTICE

Although the number of clinically relevant DDIs is probably low, DDIs may be responsible for a substantial number of hospital admissions. Therefore the pharmacist is responsible for preventing the use of unsafe or non-effective drug regimens. Specifically, pharmacists should avoid the dispensing of combinations of drugs that may cause serious DDIs (Becker *et al.*, 2005:371).

Many drug interactions can be avoided or managed safely if adequate time and precautions are taken by a patient's pharmacist. Having the pharmacist provide patient counselling on the use of prescription and non-prescription medication, disease state(s), and the safety of concurrent use of herbal products plays a major role in avoiding drug interactions (Brown, 2004).

According to Lien and Lien (1994: 371), many patients visit more than one doctor for their different diseases and receive more than one drug at a time, and often doctors are unaware of all the medications their patients

are taking and the risks to which their patients are exposed when treated with multiple drugs. Since pharmacists in the community setting or hospital, are the most accessible health care providers, they are able to intervene when faced with potential drug interactions that may occur during patients' multiple drug therapy.

Adverse DDIs are the major cause of morbidity and mortality. Cancer patients, for example, are particularly at high risk of such interactions because they commonly receive multiple medications, including cytotoxic chemotherapy, hormonal agents and supportive care drugs (Blower *et al.*, 2005:117). Increased awareness by pharmacists of the potential for drug interactions will allow health care providers to minimise the risk by selecting appropriate drugs and also by monitoring for signs of interaction.

According to Pezella (2005:49), in 2000, the number of patient deaths attributable to ADRs in the United States of America, was estimated to be 218 000 annually. More than 51% of approved drugs in the market in 2009 may have serious side-effects not detected before marketing approval. Therefore health plans and pharmacy benefit managers must work together to take effective steps to increase ADR monitoring and reporting and to proactively avoid ADRs through pharmacy management tools.

2.14 CLINICAL MANAGEMENT OF DDIs

Clinical management of DDIs should include prospective and concurrent patient-, disease- and drug-monitoring measures that are sensitive enough to alert the pharmacist or health care provider to monitor specific patient-, disease- or drug-therapy parameters and, whenever possible, correlate these findings with clinical laboratory tests (Brown, 2004).

Patients at high risk for drug interactions who also take drugs with narrow therapeutic index should be monitored more closely for drug interactions, especially when a new drug is added or discontinued. Depending on the drugs in question, likely drug interactions will generally occur within a few days following a change in drug regimen. For example, drugs used for dyspepsia are known to interact with the PIs reducing their absorption, leading to lower plasma PI concentration and the potential development of virological failure (Winston & Boffito, 2005:2). A form of managing this drug interaction is not to prescribe the known drugs together. On the other hand, in the case of buffered drugs that alter gastric acidity or H_2-receptor antagonists, the two drugs should be administered as far apart as possible.

Another example is when antituberculous agents are prescribed with ARVs primarily the PIs. There is a high potency for clinically relevant negative drug interactions between PIs and rifamycins (Piscitelli & Gallicano,

2001:984). Such interaction may be managed by appropriate dose adjustments. For example, to adequately adjust for interactions between ritonavir boosted PIs and rifabutin, the latter should be decreased to 150 mg daily or 300 mg three times per week (Pozniak *et al.*, 2003:1).

Metabolic disturbances associated with HIV infection and PI therapy are common and according to Fitchenbaum *et al.* (2002b:569), the potential for significant drug interactions associated with lipid lowering agents, such as HMG-CoA reductase inhibitors and PIs is high. Therefore lactone drugs like lovastatin and simvastatin should not be co-administered with PIs, as they are avid substrates for CYP3A4 and as such their metabolism is inhibited by ritonavir, a CYP3A4 inhibitor (Fitchenbaum *et al.*, 2002b:569).

Physicians should be cautious when prescribing oral contraceptives to patients receiving PIs because of the variations in effect on ethinyl oestradiol levels. One published study by Ouellet *et al.* (1998:111) found that ethinyl estradiol area under the time concentration curve was reduced by 41% during concomitant ritonavir. Similar results were reported by Back (2005) with nelfinavir and lopinavir/ritonavir. Therefore, women receiving these drugs should use alternative forms of birth control.

Other drugs like ketoconazole and other azole antifungal drugs inhibit CYP3A4 metabolism and P-glycoprotein function and result in an increase in PI plasma exposure. This interaction is managed by substituting ketoconazole with fluconazole which is currently the best option for use with PIs (Winston & Boffito, 2003:4).

DDIs between PIs and antiepileptic medications may be complex. It has been reported by Back (2005) that the presence of ritonavir as part of the ARV combination may increase the plasma concentrations of carbamazepine, but decrease lamotrigine and valproic acid, through the different effects (inhibition and induction) exerted on different CYP450 isoenzyme responsible for the metabolism of the drugs. Since the clinical significance of this interaction is unknown, therapeutic drug monitoring of both antiepileptic and ARV agents should be performed when the two drugs are combined.

Drug interactions are known to occur when PIs are used concomitantly with herbal remedies such as St John's Wort, garlic supplements and Echinacea (Back, 2005). When combining herbal therapies with ARV agents, extreme caution is required.

Managing drug interactions will be more likely to occur when the pharmacist takes time and utilises an adequate patient data base that includes the patient's gender, age, vital signs, medical diagnoses, drug allergies, relevant laboratory tests, and a complete listing of medication being taken routinely or taken on an

as-needed basis. If the pharmacist lacks essential patient data, he/she may obtain it from the patient. In addition, with the patient's permission, the pharmacist may call the physician to get essential monitoring information, such as results of recent laboratory tests or a complete list of medical diagnoses (Brown, 2004).

While most DDIs involving HIV drugs are essentially unavoidable, many can be better managed, e.g. dose adjustment to manage efavirenz-based interactions have been associated with significant reductions in HIV viral load. The identification of clinically significant DDIs is fundamental to improving the quality of prescribing in HIV management. Studies have shown that physician awareness of DDIs is poor: less than half of clinically significant DDIs were recognised by physicians in a survey of 159 consecutive patients receiving ARVs (Evans-Jones *et al.*, 2009:51).

As coverage of ART increases, a programmatic approach could be taken on national or regional level to improve vigilance for and recognition of important DDIs (Kigen *et al.*, 2008:7). In areas where disease epidemiology overlaps, protocols for the treatment of co-infection could be incorporated into existing ARV programmes, taking into account local drug availability.

2.15 CHAPTER SUMMARY

In this chapter, the national and international management of HIV/AIDS was discussed in detail. The second part of this chapter covered an overview of DDIs as a subset of adverse drug events. A discussion on possible causes of, general incidence and frequency of DDIs, plus the diseases and drugs at high risk for DDIs was also included. The pharmacological aspects of DDIs of ARVs, risk factors for DDIs with ARV agents were discussed and finally a discussion on the role of a pharmacist in preventing and managing DDIs in clinical settings was discussed.

CHAPTER 3

RESULTS

In this section the general findings of the study are discussed in the different research articles as indicated in Section 1.5.10.

ARTICLE 1:

Prevalence of drug-drug interactions of antiretroviral agents in the private health care sector in South Africa. 2008. *South African Medical Journal*, 98(2):109-113

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Prevalence of drug-drug interactions of antiretroviral agents in the private health care sector in South Africa

N L Katende-Kyenda, M S Lubbe, J H P Serfontein, I Truter

Objectives. Human immunodeficiency virus (HIV) infection can be effectively treated with highly active antiretroviral therapy (HAART), requiring concomitant administration of three to four different agents, often with a high potential for drug-drug interactions (DDIs). This study aimed to determine the prevalence of possible DDIs between antiretrovirals (ARVs) themselves and other drugs.

Design. Retrospective drug utilisation study using data from a national medicine claims database for the period 1 January to 31 December 2004.

Setting. A section of the private health care sector in South Africa.

Subjects. All ARV prescriptions (*N*=43 482) claimed during 2004. The possible DDIs found were classified according to a clinical significance rating described by Tatro (2005) in his book *Drug Interaction Facts.*

Results. A total of 5 305 882 medicine items were prescribed; of these, 1.92% (*N*=101 938) were ARVs. Of the total number of 2 595 254 prescriptions, 1.68% (*N*=43 482) contained ARVs. A total number of 18 035 DDIs (81 different types) were identified; of these, 83.89% (*N*=15 130) were DDIs between ARVs and other drugs, while 16.11% (*N*=2 905) were DDIs between ARVs themselves. Possible DDIs with a clinical significance level of 1 (major, *N*=17) and 2 (moderate, *N*=1 436) represented 8.06% (*N*=1 453) of the total number of identified interactions.

Conclusions. Since concomitant use of ARVs and other drugs used to treat HIV complications is increasing, there is a need to understand and anticipate these DDIs and to overcome them by dose adjustments and patient education, so that they are not life threatening to HIV/AIDS patients.

S Afr Med J 2008; 98: 109-113.

Human immunodeficiency virus (HIV) infection can now be effectively treated with the use of combination therapy, described as highly active antiretroviral therapy (HAART), requiring concomitant administration of three or four different agents, with a high potential for drug-drug interactions (DDIs)[1] and adverse drug reactions (ADRs).[2] HAART consists of a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one or two protease inhibitors (PIs), decreasing morbidity and mortality[3] from opportunistic infections and making HIV infection a chronic disease.

HIV-infected individuals usually have an impaired immune response, and frequently develop opportunistic infections, malignancies, co-morbidity such as drug dependence, psychiatric disorders, and neurological manifestations of HIV or hepatic diseases, treatment of which requires a wide variety of drugs.[4] Since both NNRTIs and PIs are extensively metabolised by the cytochrome P450 (CYP) system[5] there is considerable potential for pharmacokinetic interactions when these drugs are administered concomitantly with drugs metabolised via the same pathway.

The complexity of the drug regimen poses a significant challenge, in that there is a potential for a great number of DDIs. Antiretroviral (ARV) combinations can result in enhanced therapeutic efficacy, while others may augment the toxicity.[6] To help the patient safely and effectively navigate the array of doses and drugs, the HIV/AIDS care provider should therefore have a comprehensive understanding of the key issues affecting the pharmacokinetic and pharmacodynamic effects of drug therapy, thus minimising DDIs and ADRs.

The prevalence of DDIs in ARVs has not yet been investigated in depth in private health care settings in South Africa. The aim of this study was therefore to determine the prevalence of possible DDIs between ARVs themselves and other drugs on prescriptions claimed for the year 2004.

Methods

Study design

Permission to conduct the study was granted from Interpharm Datasystems and approved by the Research and Ethics Committees of North-West University, Potchefstroom campus, and Walter Sisulu University, Mthatha campus. This was a retrospective drug utilisation study done on ARVs claimed

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through a national medicine claims database for the period 1 January 2004 to 31 December 2004. During 2004, this medical scheme administrator administered data for 80 medical schemes. The focus of this study was on the prevalence of possible DDIs between ARVs themselves and other drugs on the same prescription. The possible DDIs found in this study were classified according to a clinical significance rating expressed as a number assigned to each DDI based on the severity and documentation of the interaction, as follows: 1 (major), 2 (moderate), 3 (minor), 4 (major/moderate) and 5 (minor/any), as described by Tatro.[7]

Three degrees of severity were identified, namely major, moderate and minor:[7]

- **Major effects** are potentially life threatening, capable of causing permanent damage, and necessitating additional treatment, hospitalisalisation or extension of hospital stay.
- **Moderate effects** may cause deterioration of a patient's clinical status, requiring additional treatment, hospitalisation or extension of hospital stay.
- **Minor effects** are usually mild, having bothersome or unnoticeable consequences but not significantly affecting the therapeutic outcome. Additional treatment is usually not required.

The following documentation levels can be distinguished, namely established, probable, suspected, possible and unlikely. The scale represents an evaluation of the quality and clinical relevance of the primary literature supporting the occurrence of an interaction.[7] Drug interactions assigned documentation levels of established, probable, or suspected are considered to be well substantiated and have significance ratings of 1, 2 or 3. These interactions are considered probable, while interactions of significance ratings 4 or 5 are not substantiated, having documentation levels of possible or unlikely.

Study population

The study population consisted of all ARV prescriptions (*N*=43 482) claimed during 2004.

Study protocol

The data consisted of ARV drug names and others prescribed on the same prescription. The ARVs were classified according to pharmacological groups as described in the *Monthly Index of Medical Specialties* (*MIMS*).[8] Drug interactions were detected using a previously developed computerised drug interaction database system.

According to the Medicines Control Council of South Africa,[9] 14 ARVs (NRTIs, NNRTIs and PIs) were registered during the period 1989 - 2004.

Statistical analysis

The data were obtained directly from the Interpharm Datasystems and analysed using the Statistical Analysis System, SAS 9.1.[10] There was no direct manipulation of the data by the researcher. Research was conducted on the assumption that all data obtained from the medicine claims database were correct and accurate. Data for the analysis were obtained from one medicine claims database, thus limiting external validity, and implying that results can only be generalised to the specific database used, as well as to the specific study population. No specific patient, medical practice, pharmacy or medical scheme could be identified; confidentiality of information was thus maintained throughout the study.

Results

A total of 5 305 882 medicine items were prescribed; of these, 1.92% (*N*=1 01 938) were ARVs. Of the total number of 2 595 254 prescriptions, 1.68% (*N*=43 482) contained ARVs. A total number of 18 035 DDIs (81 different types) were identified; of these, 83.89% (*N*=15 130) were DDIs between ARVs and other medications, while 16.11% (*N*=2 905) were DDIs between ARVs themselves. Possible DDIs with a clinical significance level of 1 (major, *N*=17) and 2 (moderate, *N*=1 436) represented 8.06% (*N*=1 453) of the total number of identified interactions. The frequencies of level 3 to 5 interactions were: 3 – *N*=1 221; 6.77%, 4 – *N*=6 678; 37.03%, and 5 – *N*=8 683; 48.14%. Level 1 interactions were between: (*i*) indinavir and lanzoprazole (*N*=3; 17.65%), omeprazole (*N*=2; 11.76%) and simvastatin (*N*=1; 5.88%); (*ii*) ritonavir and simvastatin (*N*=4; 23.53%), digoxin (*N*=5; 29.41%) and fentanyl (*N*=1; 5.88%); and (*iii*) saquinavir and fentanyl (*N*=1; 5.88%). The most prevalent (more than 100) level 2 DDIs between ARVs themselves were: indinavir and ritonavir (*N*=490), efavirenz and ritonavir (*N*=274), efavirenz and indinavir (*N*=198), didanosine and indinavir (*N*=121) and efavirenz and lopinavir/ritonavir (*N*=118), as set out in Table I. Level 2 interactions between ARVs and other drugs are set out in Table II.

Discussion

The aim of this study was to determine the prevalence of possible DDIs between ARVs themselves and other drugs on prescriptions claimed in a section of the private health care sector in South Africa. This study indicated that the prescriptions of ARVs accounted for 1.68% (*N*=43 482) of the total number of prescriptions (*N*=2 595 254) claimed from the database. Eighty-one different types of DDIs were identified; of these 83.89% (*N*=15 130) were DDIs between ARVs and other medications, and 16.11% (*N*=2 905) were between ARVs themselves. HIV-infected individuals usually receive a wide variety of drugs in addition to their ARV drug regimen. Since both NNRTIs and PIs are extensively metabolised by the cytochrome P450 system, there is a considerable potential for pharmacokinetic drug interactions when they are administered concomitantly with other drugs metabolised via the same pathway. In addition, PIs are substrates as well as inhibitors of the drug transporter plasma membrane glycoprotein (P-

Table I. Frequency of level 2 interactions between ARVs themselves

ARVs interacting between themselves	*N*	%*
Indinavir (PI) and ritonavir (PI)	490	36.95
Efavirenz (NNRTI) and ritonavir (PI)	274	20.66
Efavirenz (NNRTI) and indinavir (PI)	198	14.93
Didanosine (NRTI) and indinavir (PI)	121	9.13
Efavirenz (NNRTI) and lopinavir/ritonavir (PI)	118	8.90
Efavirenz (NNRTI) and saquinavir (PI)	1	0.08
Efavirenz (NNRTI) and saquinavir (PI)	1	0.08
Nevirapine (NNRTI) and lopinavir/ritonavir PI)	49	3.70
Nelfinavir (PI) and nevirapine (NNRTI)	2	0.15
Nevirapine (NNRTI) and saquinavir (PI)	5	0.38
Nevirapine (NNRTI) and ritonavir (PI)	3.39	
Indinavir (PI) and lopinavir/ritonavir (PI)	9	0.68
Indinavir (PI) and nevirapine (NNRTI)	13	0.98
Total	1 326	100.00

*Percentages were calculated according to the total number of interactions presented.
NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Table II. Frequency of level 2 interactions between ARVs and the other drugs

Interacting ARVs and other drugs	*N*	%*
Didanosine + ketoconazole	1	0.91
Didanosine + ofloxacin	1	0.91
Didanosine + ciprofloxacin	2	1.82
Didanosine + iraconazole	3	2.73
Didanosine + ketoconazole	2	1.82
Efavirenz + alprazolam	6	5.45
Efavirenz + methadone	4	3.64
Efavirenz + triazolam	4	3.64
Indinavir + fluconazole	7	6.36
Indinavir + itraconazole	7	6.36
Indinavir + ketoconazole	4	3.64
Lopinavir + fluconazole	2	1.82
Lopinavir + itraconazole	2	1.82
Lopinavir/ritonavir + alprazolam	1	0.91
Lopinavir/ritonavir + chlordiazepoxide	3	2.73
Lopinavir/ritonavir + diazepam	1	0.91
Lopinavir/ritonavir + fluconazole	15	13.64
Lopinavir/ritonavir + itraconazole	2	1.82
Ritonavir + alprazolam	3	2.73
Ritonavir + chlordiazepoxide	3	2.73
Ritonavir + diazepam	1	0.91
Ritonavir + fluconazole	16	14.55
Ritonavir + itraconazole	2	1.82
Ritonavir + fluoxetine	2	1.82
Ritonavir + piroxicam	2	1.82
Ritonavir + pravastatin	2	1.82
Ritonavir + zolpidem hemitartate	3	2.73
Saquinavir + chlordiazepoxide	2	1.82
Saquinavir + diazepam	1	0.91
Saquinavir + fluconazole	2	1.82
Saquinavir mesylate + fluconazole	2	1.82
Saquinavir mesylate + alprazolam	2	1.82
Total	110	100.00

*Percentages were calculated according to the total number of interactions presented.

gp) that can result in pharmacokinetic drug interactions. The NRTIs are predominantly excreted by the renal system and may give rise to interactions.[4]

Possible DDIs with a clinical significance level of 1 (*N*=17) and 2 (*N*=1 436) represented 8.06% (*N*=1 453) of the total number of possible interactions identified in this study. Level 1 interactions were between (*i*) indinavir and lanzoprazole, omeprazole and simvastatin; (*ii*) ritonavir and simvastatin, digoxin and fentanyl; and (*iii*) saquinavir and fentanyl.

Indinavir and ritonavir are PIs, inhibitors of the CYP 3A4 enzyme that is important for the metabolism of several drugs, which increases the probability of pharmacokinetic interactions between PIs and drugs taken concomitantly. The interaction between ritonavir and simvastatin is supported by Clotet and Negredo,[11] who report that PI administration may be associated with alterations in plasma lipids and insulin levels, placing some PI-treated patients at increased risk for coronary heart disease. Statins are an important component of pharmacotherapy for PI-associated dyslipidaemia, but, because all except pravastatin are metabolised by the CYP450 enzyme system, concomitant use of these agents produces a substantial risk of drug interactions and statin-induced hepatotoxicity and myopathy.[1] Fortunately new PIs are available that do not adversely affect plasma lipid levels.

Interactions between ritonavir and digoxin accounted for 29.41% (*N*=5) of possible level 1 DDIs in this study. Ritonavir has been reported to decrease total digoxin clearance at renal and non-renal levels,[12] and therapeutic doses of ritonavir also inhibits drug transport and metabolism in humans. Concomitant use of ritonavir with digoxin, a P-gp substrate, therefore requires major dose adjustments.

In this study interaction of ritonavir with fentanyl accounted for 5.88% (*N*=1) of possible level 1 reactions. Among HIV PIs, ritonavir is the most potent inhibitor of CYP3A4. Fentanyl, a synthetic opioid analgesic is metabolised mainly by CYP3A4. A study[13] revealed that ritonavir profoundly affected the pharmacokinetics of fentanyl, reducing its clearance by 67% and increasing and prolonging fentanyl-induced respiratory depression. It is therefore advisable to maintain respiratory monitoring for longer than usual in patients on these two drugs.

Combinations of ARVs are being used to augment and prolong their virological and immunological benefits, and also to delay the emergence of resistance. ARVs, especially the PIs, have a strong potential to interact with each other. In particular, the NNRTIs metabolised by CYP3A4 have shown to interact with PIs, which are inhibitors of CYP3A4, especially ritonavir, a potent inhibitor. In our study interactions between indinavir and ritonavir accounted for 36.95% (*N*=490) of possible level 2 DDIs between ARVs themselves. Administration of ritonavir improves the bioavailability and prolongs the elimination half-life of indinavir, reducing the total dose necessary to achieve a potent ARV plasma concentration. It is therefore recommended that patients be closely monitored so that the dose can be adjusted when necessary.

This study revealed a possible DDI between ritonavir and efavirenz, with a prevalence of 20.66% (*N*=274) of possible level 2 DDIs between ARVs themselves. An interaction between ritonavir and efavirenz has been reported[13] in 20 healthy volunteers who received efavirenz 200 mg daily and ritonavir up to 600 mg twice daily. With this combination, the area under the curve (AUC) for efavirenz increased by 21% and that for ritonavir by 17%, leading to the conclusion that if patients experience intolerance to ritonavir while on efavirenz, the ritonavir dosage could be reduced to 500 mg twice daily.

Interactions between efavirenz and indinavir accounted for 14.93% (*N*=198) of possible level 2 DDIs between ARVs themselves in our study. This finding is supported by a study[14] reporting that the addition of efavirenz to a combination of 800 mg indinavir and 100 mg ritonavir twice daily resulted in significant decreases in AUC, C_{max}, and especially C_{min} of indinavir. Efavirenz is a potent inducer of CYP3A4, suggesting a potential interaction between this NNRTI and PIs that inhibit CYP3A4. It is recommended that the dose of indinavir or ritonavir be increased to maintain indinavir drug levels when efavirenz is added to the indinavir-ritonavir combination.

Interactions of didanosine with indinavir accounted for 9.13% (*N*=121) of possible level 2 DDIs between ARVs themselves in our study. Various combinations of NRTIs and PIs are acceptable as HAART to overcome the induction of PI metabolism by the NRTIs, administration of indinavir and didanosine separately at least 1 hour apart on an empty stomach is therefore recommended.

Drugs used to treat opportunistic infections could influence the occurrence of ADRs to ARVs. In this study the azoles (ketoconazole, fluconazole and itraconazole), used to treat fungal infections, interacted with PIs at level 2. A patient taking ritonavir 600 mg twice daily and saquinavir 400 mg twice daily is reported to have developed symptoms of PI toxicity 1 week after itraconozole was increased from 100 mg to 200 mg twice daily,[15] and 2 of 4 patients receiving indinavir developed hyperbilirubinaemia and slightly elevated transaminase levels while on itraconazole. Levels returned to pretreatment values after discontinuing itraconazole. Fluconazole is a less potent inhibitor of CYP3A4, so may be a better tolerated alternative.

The PIs in this study interacted with benzodiazepines at level 2. Large increases in serum concentrations of benzodiazepines undergoing oxidative metabolism due to inhibition of hepatic metabolism (CYP3A4) may cause severe sedation and respiratory depression. Prolonged sedation was reported in a 32-year-old patient receiving intravenous midazolam for bronchoscopy after administration of saquinavir but not after midazolam alone.[16] Co-administration of PIs with benzodiazepines is therefore contraindicated.

Conclusion

In this study DDIs have been identified between ARVs themselves and between ARVs and other drugs. Managing these DDIs is one of the major challenges associated with the multidrug regimens used for HIV therapy. Some of these DDIs can be overcome by dose adjustments and by advising the patient to take some drugs separately. Other DDIs are not considered clinically life threatening.

Limitations of the study

The followings should be taken into consideration when evaluating these results.

- Only the prescription data were available to the researchers. It was not possible to gain any demographic or clinical information on the patients.
- The clinical relevance of the identified DDIs was evaluated according to criteria stated in the literature. No clinical evaluation of the real effects of these interactions was possible. However, the results emphasised the possibility of DDIs that could have led to severe problems. Further research into the usage of ARVs in the private health care sector should therefore be conducted in South Africa.
- Various combinations of NNRTIs and PIs are acceptable as HAART, with dosage adjustments of PIs, but in this study dosage adjustments were not investigated; we therefore recommend that further studies be done.

The financial assistance of the Medical Research Council (MRC) and National Research Foundation (NRF) towards the research is hereby acknowledged. Opinions expressed in this paper, and the conclusions arrived at, are those of the authors and not necessarily to be attributed to the NRF or the MRC. Thanks also to the managers of the private primary health care service provider that provided the data and to Mrs Mèlane Terblanche for assisting in proofreading the manuscript.

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Accepted 13 July 2007.

ARTICLE 2:

Effect of Prescribed Minimum Benefits on the prevalence of drug-drug interactions of antiretroviral agents in a section of the private health care sector in South Africa: A two-year comparative study. 2008. *International journal of pharmacy practice,* 16:403-408.

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IJPP
International Journal of
Pharmacy Practice

IJPP 2008, 16: 403–408
© 2008 The Authors
Received November 15, 2007
Accepted July 16, 2008
DOI 10.1211/ijpp.16.6.0010
ISSN 0961-7671

Effect of prescribed minimum benefits on the prevalence of possible drug–drug interactions of antiretroviral agents in a section of the private health care sector in South Africa: a 2 year comparative study

Norah L. Katende-Kyenda, Martie S. Lubbe, Jan H.P. Serfontein and Ilse Truter

Abstract

Objective The aim of this study was to determine the impact of prescribed minimum benefits (PMBs) after implementation, on the prevalence of possible drug–drug interactions (DDIs) between antiretrovirals (ARVs) themselves and other drugs on prescriptions claimed in a section of the private health care sector in South Africa.

Setting A section of the private health care sector in South Africa.

Method A comparative, retrospective drug-utilisation study was performed using 2004 and 2005 data from a medicine claims database. Possible DDIs found were classified according to Tatro (2005).

Key findings The data consisted of 43 482 ARV prescriptions claimed during 2004 and 51 613 for 2005. A total of 5 305 882 and 3 606 992 medicine items were claimed during 2004 and 2005 respectively, of which 1.92% were ARVs for 2004 and 3.38% for 2005. Of 18 035 DDIs identified, 83.89% were between ARVs and other medications, and 16.11% were between ARVs themselves for 2004. Of 25 130 DDIs identified for 2005, 92.59% were between ARVs and other medications, and 7.41% were between ARVs themselves.

Conclusions The decrease in DDIs between ARVs alone for 2005 as compared to 2004 could indicate a possible impact of PMBs on HIV/AIDS, as a chronic disease in which management programmes were introduced to ensure the appropriateness and effectiveness of drugs in HIV/AIDS. It is therefore recommended that further investigations be done on the management of the most important DDIs between ARVs alone and other drugs prescribed on the same prescription.

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Acknowledgments: The financial assistance of the South African Medical Research Council and the South African National Research Foundation towards the research is hereby acknowledged. Opinions expressed in this paper, and conclusions arrived at, are those of the authors. Thank you to the managers of the medicines claims database that provided the data and to Mrs M. Terblanche for assisting in proofreading the

Introduction

HIV infection represents a major medical problem worldwide, affecting more than 42 million people.[1] Of these, 25 million reside in sub-Saharan Africa.[2] According to the mid-2007 estimates from Statistics South Africa, with a population of approximately 47.9 million,[3] over 5 million individuals in South Africa are infected.[1] The chronic nature of HIV infection requires lifelong highly active antiretroviral therapy (HAART)[4] to continuously suppress HIV-1 viral replication, thus reducing morbidity and mortality.[5] HAART is restricted by treatment barriers such as complex dosing, drug–drug interactions (DDIs) and toxicities, leading to patient non-adherence, with subsequent treatment failures and development of resistant strains.[6] Thus, it remains a challenge to achieve adequate and sustained viral suppression while on treatment with HAART.

HAART consists of combinations such as two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), three NRTIs, or two NRTIs and a protease inhibitor (PI). The antiretroviral (ARV) agents available in South Africa are divided into three therapeutic classes: NRTIs that include zidovudine (AZT), lamivudine (3TC), abacavir, stavudine (d4T), didanosine (ddI) and zalcitabine; NNRTIs including nevirapine (NVP) and efavirenz (EFV); and PIs including nelfinavir, indinavir, ritonavir (RTV), saquinavir in hard or soft gel capsule form, amprenavir and lopinavir (LPV).[7]

On April 22, 2002, the World Health Organization issued its first treatment guidelines

World Health Organization endorsed the inclusion of ARVs in the Core List of its Model Essential Medicine List, which "presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost effective medicines for priority conditions".

The South African guidelines for the use of ARV regimens in adults include (1a) d4T plus 3TC plus EFV, (1b) d4T plus 3TC plus NVP and (2) AZT with ddI and LPV/RTV. AZT and 3TC are listed as the initial recommendation for the dual NRTI component based on the efficacy, toxicity and clinical experience, as well as the availability of the medicines in a fixed-dose combination. Other NRTIs may substitute the AZT/3TC dual NRTI component as first-line regimens. However, AZT/3TC would then be required as potential components for second-line regimens.[9]

HAART has a high potential for DDIs, and in addition some HIV-positive patients still require concomitant treatment with drugs for opportunistic infections, some require medication to treat unrelated medical conditions and/or the metabolic complications of ARV therapy[10] and others may self-medicate with herbal formulations and/or over-the-counter drugs.[11] Therefore, the virtually limitless number of drug combinations that may be taken by patients undergoing treatment of HIV infection makes DDIs almost inevitable. This is one of the major challenges associated with the multidrug regimens used for HIV therapy.

The Medical Schemes Act (Act 131 of 1998), effective from January 2000, regulated medical scheme coverage for certain defined health conditions in terms of prescribed minimum benefits (PMBs),[12] that were introduced on 1 January 2004 into the health care sector.[13] These are benefits in respect of relevant health services prescribed by regulations under the act, and consist of a list of 27 identified chronic conditions that constitute the Chronic Disease List (CDL). Each chronic condition has a detailed treatment protocol that has been published in the *Government Gazette*.[12] The objectives of the PMB regulation are to avoid incidents where individuals lose their medical scheme coverage in the event of serious illness and the consequent risk of unfunded utilisation of public hospitals, and to encourage improved efficacy in the allocation of private and public health care resources.[14]

On January 2005, all medical schemes had to provide benefits for members with HIV/AIDS, according to the amendment of the Medical Schemes Act of 1998.[12] PMBs are reviewed at least every 2 years, focusing specifically on the development of protocols for medical management of HIV/AIDS. According to the new amendment, all patients have a right to the following treatments:[15] HIV voluntary counselling and testing, co-trimoxazole as a preventive therapy, ARV therapy, screening and preventive therapy for tuberculosis, diagnosis and treatment of sexually transmitted infections, pain management in palliative care, treatment of opportunistic infections which include *Pneumocystis carinii* pneumonia (PCP), tuberculosis and oral thrush, prevention of mother-to-child transmission of HIV, post-exposure prophylaxis following occupational exposure or sexual assault, and medical management and medication, including the provision of ARVs, and ongoing monitoring for medicine effectiveness and safety, to the extent provided for in the national guidelines applicable in the public sector.

The prevalence of DDIs in ARVs has not yet been investigated in depth in the private health care sector in South Africa, with respect to the possible influence in the wake of the implementation of PMBs on the prevalence of DDIs. Therefore, the aim of this study was to determine and compare the prevalence of possible DDIs between ARVs alone and other drugs on prescriptions claimed for 2004 and 2005. The results will provide information on the prevalence of possible DDIs in ARV prescriptions and the possible impact of implementation of PMBs.

Methods

A retrospective drug-utilisation study was done on ARV prescriptions claimed through a national medicine claims database of a medical scheme administrator in the private health care sector of South Africa for the period January 1 to December 31, 2004 and January 1 to December 31, 2005. This company is an organization that manages the benefits of certain section of medical schemes and insurance companies in South Africa by providing a real-time auditing process to claims from pharmacies and service providers. In 2004, this company performed claim switching for 50% of South Africa's medical providers,[16] and for 68 medical aid schemes in 2005. The number of medical schemes covered in 2005 was lower, as was reflected in the lower numbers of medicine items and prescriptions claimed. There are various medical scheme administrators in South Africa and a medical scheme can decide whether a medicine scheme administrator should manage its benefits or they could do it themselves.

Each prescription record contained a unique number to identify each patient, medical practice, pharmacy or medical scheme. No specific patient, medical practice, pharmacy or medical scheme could be identified; thus confidentiality of information was maintained throughout the study. Data were analysed by using SAS version 9.1.[17]

The data-set consisted of the following information: (1) a specific code for the medical scheme (i.e. the specific medical scheme could not be identified), (2) medical scheme member number, (3) dependent (patient's) number, (4) prescription number, (5) date of dispensing the prescription, (6) trade name of the medicine item, (7) Nappi code of the medicine item (a Nappi code is a unique nine digit number implemented with electronic transactions in mind; it is unique for each product name, pack size, strength, manufacturer and exclusions)[18], (8) amount of the medicine item prescribed and (9) amount paid by the medical scheme.

For the purpose of this study a drug item (medicine item) is defined according to the Medicines and Related Substances Control Act of 1965, Act 101 of 1965[19] as "substance intended for use in the diagnosis, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man". In this research the words 'drug items' are used interchangeably with the words 'medicine items'. In the South African context, a prescription can consist of one or more medicine (or drug) items.

The focus of this study was to determine the prevalence of possible DDIs between ARVs themselves and other medications prescribed on the same prescription and the possible impact of the implementation of PMBs on the prevalence of possible DDIs. The possible DDIs found were classified according to a clinical significant rating, and the formulae for the clinical significance ratings of DDIs are described in the form of three degrees of severity, identified as major, moderate and minor, as described by Tatro.[20] Drug interactions that are assigned documentation levels of established, probable or suspected are considered to be well substantiated and have significance ratings of 1, 2 or 3. These interactions have a probability of occurring, whereas interactions of significance ratings 4 or 5 are not substantiated, having documentation levels of possible or unlikely.

The data for the study consisted of all ARV prescriptions claimed during 2004 (n = 43 482) and 2005 (n = 51 613). 2004 was the year before the PMBs were implemented for HIV/AIDS in South Africa and 2005 was the year after the PMBs for HIV/AIDS were implemented. The data consisted of ARV drug names and other drug names prescribed on the same prescription, which were classified according to the pharmacological groups as described in the *Monthly Index of Medical Specialties* (MIMS).[18]

Permission to conduct the study was granted from the medical scheme administrator and approval was obtained from the Research and Ethics Committees of the North-West University, Potchefstroom campus and the Walter Sisulu University, Mthatha campus.

Results

Totals of 5 305 882 and 3 606 992 medicine items were claimed during 2004 and 2005 respectively. For 2004, 1.92% medicine items accounted for ARVs and 3.38% in 2005. Of the total number of 2 595 254 prescriptions (for the year 2004), 1.68% included ARVs. For 2005, the total number of prescriptions was 1 621 736 of which 3.18% included ARV prescriptions (Table 1).

For the year 2004, a total of 18 035 DDIs (81 different types) were identified between ARVs and other drugs; of these, 83.89% were DDIs between ARV drugs and other medications, while 16.11% were DDIs between ARV drugs themselves. DDIs with a clinical significance level 1 (major, n = 17) and 2 (moderate, n = 1436) represented 8.06% of the total number of identified interactions. The frequencies of interactions of levels 1–5 for 2004 and 2005 are shown in Table 2. As demonstrated in Table 2, there was a decrease in the number of possible DDIs with clinical levels 1–3 in 2005, and an increase in DDIs of levels 4 and 5.

Possible level 1 interactions identified for 2004 were between (1) indinavir and lansoprazole, omeprazole or simvastatin, (2) ritonavir and simvastatin, digoxin or fentanyl and (3) saquinavir and fentanyl (Table 3). Possible level 2 interactions identified between ARVs and other drugs for 2004 and 2005 are demonstrated in Table 4. The most prevalent (more than 100) DDIs of clinical significance level 2 identified in prescriptions for 2004 between ARVs themselves were indinavir and ritonavir, efavirenz and ritonavir, efavirenz and indinavir, didanosine and indinavir, and efavirenz and lopinavir/ritonavir, as demonstrated in Table 5. For 2005, a total of 25 130 DDIs (44 different types) could be identified, noting an increase in the number, but a decrease in the number of types of DDIs. Of these, 92.59% were DDIs between ARVs and other drugs, whereas 7.41% were DDIs between ARVs themselves. Possible DDIs with a clinical significance level 1 (major, n = 15) and 2 (moderate, n = 504) represented 2.07% (n = 519) of the total number of identified interactions for 2005 (Table 2). Level 1 interactions identified for 2005 were between indinavir and simvastatin, and ritonavir and digoxin (Table 3).

Table 1 ARV drugs, total number of ARV prescriptions for 2004 and 2005 in terms of medicine items

Description	2004		2005	
	n	%[a]	n	%[a]
Medicine items	5 305 882		3 606 992	
ARV drug items	101 938	1.92	122 062	3.38
Total number of prescriptions	2 595 254		1 621 736	
ARV prescriptions	43 482	1.68	51 613	3.18

[a]Percentage was calculated according to the total number of ARV drugs and ARV prescriptions claimed during a specific year.

Table 2 Possible level 1–5 interactions between ARVs and other drugs for 2004 and 2005

Significance rating	Severity	Documentation	2004 (%[a]; n = 18 035)	2005 (%[a]; n = 25 130)
1	Major	Suspected or greater	0.09	0.06
2	Moderate	Suspected or greater	7.96	2.01
3	Minor	Suspected or greater	6.77	3.90
4	Major/ moderate	Possible	37.03	39.25
5	Minor/any	Possible or unlikely	48.15	54.78
Total			100.00	100.00

[a]Percentage was calculated according to the total number of possible interactions identified in a specific year.

Table 3 Possible level 1 interactions between ARVs and other drugs for 2004 and 2005

ARVs and other drugs	2004		2005	
	n	%[a]	n	%[a]
Indinavir and lansoprazole	3	18	–	
Indinavir and omeprazole	2	12	–	
Indinavir and simvastatin	1	6	6	40
Ritonavir and simvastastin	4	24	–	
Ritonavir and digoxin	5	28	9	60
Ritonavir and fentanyl	1	6	–	
Saquinavir and fentanyl	1	6	–	
Total	17	100.00	15	100.00

[a]Percentage was calculated according to the total number of possible interactions identified on prescriptions in a specified year.

Table 4 Possible level 2 interactions between ARVs and other drugs for 2004 and 2005

ARVs and other drugs	2004		2005	
	n	%[a]	n	%[a]
Didanosine and azoles	6	5.45	2	2.2
Didanosine and quinolones	3	2.73	7	7.7
Efavirenz and benzodiazepines	10	9.09	20	22.00
Efavirenz and opioid agonists	4	3.64	–	–
Efavirenz and statins	–	–	7	7.7
Efavirenz and estrogens	–	–	13	14.3
Indinavir and azoles	18	16.36	–	–
Lopinavir and azoles	4	3.64	–	–
Lopinavir/ritonavir and benzodiazepines	5	4.55	–	–
Lopinavir/ritonavir and azoles	17	15.45	15	16.5
Nelfinavir and benzodiazepines	–	–	11	12.1
Ritonavir and benzodiazepines	3	2.73	–	–
Ritonavir and estrogens	–	–	3	3.3
Ritonavir and benzodiazepines	7	6.36	–	–
Ritonavir and azoles	18	16.36	7	7.7
Ritonavir and SSRIs	2	1.82	–	–
Ritonavir and NSAIDs	2	1.82	–	–
Ritonavir and statins	2	1.82	6	6.6
Saquinavir and benzodiazepines	3	2.73	–	–
Saquinavir and azoles	2	1.82	–	–
Saquinavir mesylate and azoles	2	1.82	–	–
Saquinavir mesylate and benzodiazepines	2	1.82	–	–
Total	110	100.00	91	100.00

[a]Percentage was calculated according to the total number of possible interactions identified on prescriptions in a specific year.
SSRIs, selective serotonin-reuptake inhibitors.

As demonstrated in Table 3, there were fewer possible DDIs identified between ARVs and other drugs interacting at level 1 (major) for 2005 compared to 2004. 2005 was the year after the implementation of PMBs for HIV infection in South Africa, and certain managed care programmes were implemented to improve the management of certain chronic diseases like HIV/AIDS.

Table 5 compares the frequencies of possible DDIs between ARVs interacting at level 2 for both years. It is noted that there was an increase in DDIs for 2005, a year after the implementation of PMBs, in which many medical schemes contracted, resulting in the increase in the number of ARV prescriptions, and therefore ARV drugs (Table 1). The more drugs prescribed, the more possible DDIs would be between the drugs. As demonstrated in Table 5, the most prevalent DDIs (more than 50) of clinical significance level 2 between ARVs were identified between indinavir and ritonavir, efavirenz and lopinavir/ritonavir, efavirenz and indinavir, didanosine and indinavir, and lopinavir/ritonavir and nevirapine.

Table 4 shows the results of the frequencies of possible level 2 interactions between ARVs and other drugs prescribed together for both years. It is noted that in 2004 there were more DDIs between ARVs and other drugs prescribed for other conditions presented by HIV/AIDS patients. In 2005, there were fewer possible DDIs between ARVs and other drugs. There was also a reduction in the different types of

Table 5 Possible level 2 interactions between ARVs for 2004 and 2005

ARVs interacting	2004		2005	
	n	%[a]	n	%[a]
Indinavir (PI) and ritonavir (PI)	490	36.95	129	6.92
Efavirenz (NNRTI) and ritonavir (PI)	274	20.66	–	–
Efavirenz (NNRTI) and indinavir (PI)	198	14.93	83	4.46
Didanosine (NRTI) and indinavir (PI)	121	9.13	37	1.99
Efavirenz (NNRTI) and lopinavir/ritonavir	118	8.90	88	4.72
Nevirapine(NNRTI) and nelfinavir (PI)	–	–	12	0.64
Efavirenz (NNRTI) and saquinavir mesylate (PI)	1	0.08	–	–
Nevirapine (NNRTI) and lopinavir/ritonavir	49	3.70	37	1.99
Nelfinavir (PI) and nevirapine (NNRTI)	2	0.15	–	–
Nevirapine (NNRTI) and saquinavir mesylate (PI)	5	0.38	–	–
Nevirapine (NNRTI) and lopinavir/ritonavir	45	3.39	37	1.99
Indinavir (PI) and lopinavir/ritonavir (PI)	9	0.68	–	–
Indinavir (PI) and nevirapine (NNRTI)	13	0.98	15	0.81
Efavirenz (NNRTI) and nelfinavir (PI)	–	–	12	0.64
Ritonavir (PI) and saquinavir (PI)	–	–	974	52.28
Didanosine (NRTI) and zidovudine (NRTI)	–	–	476	25.55
Efavirenz (NNRTI) and saquinavir (PI)	1	0.08	–	–
Total	1326	100.00	1863	100.00

[a]Percentage was calculated according to the total possible number of level 2 interactions identified on prescriptions in a specific year.

Discussion

According to this study, the total numbers of medicine items and prescriptions for 2005 were less than those for 2004, due to the database covering fewer medical schemes; but there was an increase in the percentage of ARV drugs and ARV prescriptions for 2005. 2004 was a year before the implementation of PMBs for HIV/AIDS, whereas 2005, was a year after the implementation of PMBs. This could imply the effect of PMBs for HIV/AIDs implementation in South Africa. With the implementation there could possibly have been more HIV/AIDS patients registering for these PMBs, and disease-management programmes were introduced to provide a comprehensive management approach, resulting in more ARV prescriptions.

One of the strengths of this work is that the implementation of PMBs in HIV/AIDs in South Africa has had a positive impact on the management of HIV/AIDS patients; this is shown by the decrease in the number of DDIs in 2005. One possible weakness was that the DDIs were not identified before the prescriptions were dispensed to the patients; furthermore, there was no direct manipulation of the data by the researchers to analyse information like patient demographic data, clinical information or drug dosages and combinations.

The prevalence of DDIs analysed for both years was such that, for the year 2004, 81 different types of DDIs were identified as compared to 44 in 2005. As stated above, 2004 was before the implementation of PMBs, and 2005 was after implementation. Therefore, it is expected that the number of possible DDIs between ARVs would increase for 2005 because with the implementation of PMBs for HIV/AIDS,

new treatment protocols were developed. For 2004, DDIs between ARVs and other drugs accounted for 83.89%, and in 2005 the percentage escalated to 92.59%. This could be due to the fact that after the implementation of PMBs, more medical schemes registered into PMBs for HIV/AIDS, in which their patients gained access to more comprehensive programmes that were to their advantage in that a wider range of treatment opportunities opened up for patients previously excluded from certain treatments.

There was a decrease in the number of possible DDIs with clinical levels 1, 2 and 3 in 2005, and an increase in DDIs of levels 4 and 5, due to the possible influence of the implementation of PMBs on the prevalence of DDIs between ARVs and other drugs. Together with PMBs, in 2005 certain managed care programmes were phased in to ensure the appropriateness and effectiveness of drugs in the identified chronic disease.

With the implementation of PMB for HIV/AIDS in 2005, treatment protocols were developed for the medical management of HIV/AIDS, and one survey[14] showed that 92% of beneficiaries had access to ARV therapy and 90% had access to triple-combination ARV therapy. The current PMB list for HIV infection, for example, includes co-trimoxazole as a preventive therapy and treatment of *P. carinii* pneumonia,[14] pain management in palliative care and treatment of opportunistic infections like tuberculosis and oral thrush. This could explain the results in this study whereby DDIs between ARVs and co-trimoxazole presented as 78.31% for 2004, and increased to 80.19% for 2005. According to the new amendment, all patients have a right to co-trimoxazole as a preventive therapy for *P. carinii* pneumonia. DDIs between ARVs and acetaminophen used for pain management in palliative care were in 3.99% for 2004, and increased to 4.51% for 2005.

When choosing an initial regimen for the treatment of HIV, it is important to carefully consider therapeutic goals. These include choosing HAART that is likely to maximally suppress viral replication, maintain or restore immunologic function, improve the quality of life and reduce HIV-related morbidity and mortality. The results of this study revealed that possible DDIs were between PIs themselves, accounting for 36.95% for 2004 and 52.28% for 2005 (Table 5). 2005 had a higher prevalence of possible DDIs between PI regimens, as stated above; this was the year after PMB implementation, so that more medical schemes registered into the PMB for HIV/AIDS programmes, resulting in more patients getting access to HIV treatment benefits.

In this study the ARV with the most possible DDIs was ritonavir (see Table 5). Ritonavir is the most potent CYP3A4 inhibitor and, consequently, has the most possible drug interactions.[21] These findings are supported by virologic failure reported in 40–60% of patients within 1 year of initiation of an early PI-containing HAART regimen.[22] This could be attributed to the pharmacokinetic characteristics of the PIs. All currently marketed PIs – atazanavir, amprenavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir – inhibit CYP3A4,[23] decreasing the hepatic clearance of CYP3A4 substrates and increasing their plasma levels.

The concurrent administration of a PI that markedly inhibits CYP3A4, such as ritonavir, and a PI that minimally inhibits CYP3A4, such as saquinavir, substantially increases plasma concentrations of the latter.[11] Ritonavir-boosted dual-PI regimens have been explored[24] but unexpected DDIs may occur[25] and this approach has not been shown to be better than unboosted dual-PI regimens.[26] Results of this study revealed there were possible DDIs between ritonavir and saqinavir of 52.28% for 2005, and ritonavir and indinavir of 36.95% for 2004 (Table 5). In one study,[27] a large effect of ritonavir on the pharmacokinetics of saquinavir was consistent with a large reduction of saquinavir first-pass metabolism and post-absorptive clearance. Given the limited bioavailability of saquinavir in the hard gelatin capsule formulation, this DDI is expected to have implications for the use of PIs in the management of HIV infection.

Findings from this study revealed that DDIs between indinavir and simvastatin and ritonavir and simvastatin interacted at a clinical significance level of 1, as shown in Table 3. Simvastatin, lovastatin and atorvastatin are primarily metabolised by CYP3A4, an isoenzyme inhibited by HIV-1 PIs, and therefore are contraindicated with all marketed HIV-1 PIs because of the potential for significant increases in exposure and potential toxicity.[28] Therefore, simvastatin should be avoided and atorvastatin may be used with caution in patients taking ritonavir and saquinavir soft gel capsules, and pravastatin appears to be safe for concomitant use, for it does not alter the nelfinavir pharmacokinetics. It is therefore recommended that dose adjustment of pravastatin be done with concomitant use of ritonavir and saquinavir soft gel capsules.

Whereas HAART has dramatically improved the prognosis of HIV disease, it has concurrently introduced a new level of complexity in its pharmacological management. The long-term use of multiple medications to treat HIV infection, HIV-related comorbid conditions and underlying medical disorders, and the associated toxicities and side effects of these medications, has introduced the potential for numerous DDIs, as shown in Table 4.

Conclusion

From this study a conclusion can be reached that potential DDIs are frequent among outpatients who are being prescribed ARVs alone, and with other medications prescribed together, in the private health care sector in South Africa. The findings also revealed that there was a possible impact of the PMB implementation on HIV/AIDS, as a chronic disease requiring HAART. With the implementation of these benefits in South Africa, certain managed care programmes were implemented by the Medical Schemes Act specifically in the managed care of HIV/AIDS, which all service providers had to adhere to, according to an amendment of the Act (Act 131 of 1998) to ensure the appropriateness and effectiveness of drugs. In the case of the PMBs for HIV/AIDS, the reduction in DDIs between ARVs alone and other drugs prescribed together indicate the possible impact of PMBs.

Therefore, in order to effectively treat their patients and achieve desired health outcomes, this requires that clinicians who prescribe medications for HIV-infected persons understand the mechanisms of these DDIs, and know that certain ARV agents require dosage adjustment (or pharmacokinetic enhancement) when co-administered, and that some combinations are contraindicated.

Limitations and recommendations

1 Data for the analysis were obtained directly from the medicine claims database of one medical scheme administrator in South Africa, thus limiting external validity, implying that results can only be generalised to the specific database used, as well as the specific study population, and there was no direct manipulation of the data by the researchers.
2 No demographic or clinical information of the patients was given in the database.
3 The drug dosages and combinations of the different classes of ARVs were not supplied from the database. It is therefore recommended that further investigations be done on dosages and combinations of drugs in the clinical diagnoses.
4 Clinical significance levels of the DDIs on patients could not be tested in the study because the data were retrospectively obtained from the medicine claims database.

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ARTICLE 3:

Prevalence of possible drug-drug interactions between antiretroviral agents in different age groups in a section of the private health care sector setting in South Africa.

2008. ***Journal of clinical pharmacy and therapeutic,*** **33: 93-400.**

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ORIGINAL ARTICLE

Prevalence of possible drug–drug interactions between antiretroviral agents in different age groups in a section of the private health care sector setting in South Africa

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SUMMARY

Background: The chronic nature of human immunodeficiency virus (HIV) infection requires lifelong highly active antiretroviral (ARV) therapy (HAART) to continuously suppress HIV-1 viral replication, thus reducing morbidity and mortality. HAART is restricted by complex dosing, drug–drug interactions (DDIs) and toxicities.

Objective: To determine the prevalence of possible DDIs between ARV drugs in different age groups in a section of the private primary health care sector in South Africa.

Methods: A quantitative, retrospective drug utilization review was performed on 47 085 ARV prescriptions claimed through a national medicine claims database during 2006. Possible DDIs identified were classified according to a clinical significance rating as described by Tatro [*Drug Interaction Facts* 2005. St Louis, MO: Facts and Comparisons (2005)].

Results: The total number of patients who received prescriptions that were claimed through the medicine claims database was 275 424, of whom 25·11% were males, 28·28% were females and the gender of 46·61% patients was unknown. Of the total number of patients, 3·27% were HIV patients of which an average of 5·23 ± 3·86 ARV prescriptions (n = 47 085) per patient were claimed for representing 4·73% of the total number of prescriptions claimed during the study period (N = 993 804). HIV patients received an average of 2·36 ± 0·61 ARVs per prescription. Only 4·95% of the prescriptions had one ARV medicine item, 56·04% two, 37·10% three, 1·75% four and <1% had more than four.Of 960 DDIs identified, 1·88% were for patients ≤6 years, 4·27% for patients >6 years and ≤12 years, 0·63% for patients >12 and ≤19 years, 32·40% for patients <19 years and ≤40 years, 60·21% for patients <40 years and ≤60 years and 0·63% for patients >60 years with patients <40 years and ≤60 years having the highest number of DDIs and patients older than 60 years the lowest. The majority of DDIs between the ARVs presented in significance levels 2 and 4. The most important interactions were between: indinavir (IDV) and ritonavir (n = 199); efavirenz (EFV) and lopinavir/ritonavir (n = 65) and EFV and IDV (n = 60) all interacting at level 2.

Conclusion: The importance of using drug utilization study as an identification tool to provide insight into the prescribing and utilization patterns of ARV drugs, to provide optimal therapy for patients infected with HIV is emphasized.

Keywords: age-groups, antiretroviral agents, drug–drug interactions, human immunodeficiency virus patients, private health care

INTRODUCTION

The prognosis of human immunodeficiency virus (HIV) can be improved by highly active antiretroviral (ARV) therapy (HAART). Although HAART

Received 6 November 2007, Accepted 9 April 2008
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has been proved to be effective in suppressing HIV replication, decreasing morbidity and mortality associated with the virus, and improving quality of life in adults as well as infected children, the treatment of HIV together with its associated conditions remains highly complex. The combination of these drugs can present with potential drug–drug interactions (DDIs), an important cause of adverse drug reactions (ADRs) (1).

As the success of HAART ushered in a new era in the treatment of HIV-infection, it concurrently introduced a new level of complexity in its pharmacological management. The long-term use of multiple medications to treat HIV infection, HIV-related comorbid conditions and underlying medical disorders – and the associated toxicities and side-effects of these medications – has introduced the potential for numerous DDIs (2).

Highly active ARV therapy consists of combinations such as two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), three NRTIs or two NRTIs and a protease inhibitor (PI). The ARVs available in South Africa are divided into three therapeutic classes: NRTIs that include zidovudine (AZT), lamivudine (3TC), abacavir, stavudine (d4T), didanosine (ddI) and zalcitabine (ddC); NNRTIs: nevirapine (NVP) and efavirenz (EFV); and PIs: nelfinavir, indinavir (IDV), ritonavir (RTV), saquinavir (SQV) (hard gel capsule), SQV (soft gel capsule), amprenavir and lopinavir (LPV) (3).

Two ARV treatment (ART) regimens are recommended for adult use in South Africa: 1a) d4T plus 3TC plus EFV; Protocol 1b) d4T plus 3TC plus NVP; 2) AZT with ddI and LPV/RTV (4). The recommended ART regimen for paediatrics is as follows: First-line therapy: 6 months–3 years: d4T/3TC/LPV/RTV; >3-year old and >10 kg: d4T/3TC/EFV. Then the second-line therapy: 6 months–3 years: AZT/DDI/3TC; >3-year old and >10 kg: AZT/DDI/LPV/RTV (4).

Much concern surrounds DDIs in patients receiving multi-drug therapy (5). Such interactions are an important cause of ADRs and may lead to an increased risk of hospitalization and higher health care costs (6). Studies conducted in various countries report that in general rates of potential DDIs range from approximately 1% to 66% (7–9).

As DDIs may result in toxicity, treatment failure, or loss of effectiveness and can significantly affect a patient's clinical outcome, an understanding of the fundamental mechanism of HIV DDIs may allow for early detection or avoidance of troublesome regimens and prudent management if unwanted trends do develop.

The prevalence of DDIs between ARVs in patients' prescriptions in the different age groups has not been studied in the private health care sector of South Africa. Therefore, the aim of this study is to determine the prevalence of DDIs between ARVs prescribed to patients of different age groups in a section of the private health care sector in South Africa. The results of this study will provide information on which age group presents with the most DDIs between ARVs and which ARV drugs presented with the most clinically significant DDIs in the different age groups.

METHODS

Study design

Permission to conduct the study was granted from Interpharm Datasystems® and approved by the Research and Ethical Committees of the North-West University, Potchefstroom campus and Walter Sisulu University, Mthatha campus. This was a quantitative, retrospective drug utilization study performed on 47 087 ARV prescriptions claimed through a medicine claims database during the period 1 January to 31 December 2006. During 2006, this medical scheme administrator administered 36 medical schemes' data.

The focus of this study was on the prevalence of possible DDIs between ARVs prescribed to patients of different age groups. During the retrospective drug utilization study, prescriptions with more than one ARV drug were identified with the Statistical Analysis System®, SAS 9.1 (10). These prescription were then evaluated by the researcher to determine if the combination of ARVs could cause a possible DDI according to Tatro (11). The possible DDIs identified were classified according to a clinical significant rating expressed as a number, assigned to each DDI based on the severity and documentation of the interaction, and the formula expressed as 1 (major); 2 (moderate); 3 (minor); 4 (major/moderate) and 5 (minor/any) as described by Tatro (11).

Three degrees of severity were identified, namely major, moderate and minor.

Major effects. They are potentially life threatening capable of causing permanent damage. Additional treatment, hospitalization or extension of hospital stay may be necessary.

Moderate effects. They may cause deterioration of a patient's clinical status. Additional treatment, hospitalization or extension of hospital stay may be necessary.

Minor effects. They are usually mild, having bothersome or unnoticeable consequences, without significantly affecting the therapeutic outcome. Additional treatment is usually not required (11).

The following documentation levels can be distinguished namely established, probable, suspected, possible and unlikely. According to Tatro (11), the scale represents an evaluation of the quality and clinical relevance of the primary literature supporting the occurrence of an interaction. Drug interactions assigned documentation levels of established, probable, or suspected are considered to be well substantiated and have significance ratings of 1, 2 or 3. These interactions have a probability of occurring, whereas interactions of significance ratings 4 or 5 are not substantiated – having documentation levels of possible or unlikely.

As a limitation of the study it was not possible to identify newly treated patients from the sample, because no demographic and clinical information was available on the database. All prescriptions that were claimed during the study period were included and those prescriptions with more than one ARV were evaluated according to Tatro (11).

Study population

Of the study population, 8999 were HIV patients, who received 47 085 ARV prescriptions. The prevalence of DDIs was analysed according to the age groups of the patients. The following age groups were used:

Age band 1: birth to 6 years;
Age band 2: older than 6–12 years;
Age band 3: older than 12–19 years;
Age band 4: older than 19–40 years;
Age band 5: older than 40–60 years; and
Age band 6: 61 years and older.

Study protocol

The data analysed consisted of ARV drug names that were classified according to the pharmacological groups as described in the *Monthly Index of Medical Specialities* (12). During the retrospective drug utilization study, prescriptions with more than one ARV drug were identified with the Statistical Analysis System®, SAS 9.1 (10). These prescription were then evaluated by the researcher to determine if the combination of ARVs could cause a possible DDI according to Tatro (11) and other literature.

Statistical analysis

The data were obtained directly from Interpharm Datasystems® and analysed using the Statistical Analysis System®, SAS 9.1 (10). There was no direct manipulation of the data by the researcher. Research was conducted from the viewpoint that all data obtained from the medicine claims database were correct and accurate. Data for the analysis were obtained from one medicine claims database, thus limiting external validity, implying that results can only be generalized to the specific database used, as well as to the specific study population.

Each prescription record contained a unique number to identify each patient, medical practice, pharmacy or medical scheme. These numbers were randomly allocated by the medical scheme administrator providing the data to ensure confidentiality. Thus, no specific patient, medical practice, pharmacy or medical scheme could be identified. Thus, confidentiality of information was maintained throughout the study.

Results

A total 275 424 patients visited the clinic during the year 2006, of whom 25·11% were males, 28·28% were females and the gender of 46·61% patients were unknown. The age distribution of patients is given in Table 1.

Of the total number of patients, 8999 (3·27%) were HIV patients, by whom an average of

Table 1. Distribution of patients per age group (n = 275 424)

	Total database (N = 275 424)		HIV patients (N = 8999)	
Age band (years)	(n)	(%[a])	(n)	(%[a])
Birth to 6 years	29 749	10·80	171	1·90
Older than 6–12	23 451	8·51	230	2·56
Older than 12–19	21 457	7·79	76	0·84
Older than 19–40	93 273	33·87	3033	33·70
Older than 40–60	80 718	29·31	5347	59·42
Older than 60 years	16 431	5·97	142	1·58
Unknown	10 345	3·76		
Total	275 424	100	8999	100

[a]Percentage was calculated according to the total number of patients per age group.

5·11 ± 3·89 ARV prescriptions (n = 47 085) per patient were claimed during 2006. The average number of ARV prescriptions per year according to age groups is shown in Table 2. ARV prescriptions represented 4·72% of the total number of prescriptions claimed during the study period (n = 996 787). HIV patients received an average of 2·36 ± 0·61 ARVs per prescription.

The results in Table 2 demonstrate that age group 5 (older than 40–60 years) accounted for the highest number of ARV prescriptions, 55·61% of the total number of ARV prescriptions, followed by age group 4 (older than 20–40 years), with 37·58% ARV prescriptions. These results are confirmed by results in Table 1 which demonstrates that these two age groups presented the highest number of HIV patients resulting in having the highest number of ARV prescriptions. This could be explained by the fact that people in these age groups represent the working and economically active class that could afford a medical scheme and use the private health care services. Age group 3 (older than 12–19 years) had the lowest number of ARV items (0·96%) and 0·95% ARV prescriptions. Only 4·95% (n = 2332) of the prescriptions had only one ARV medicine item, 56·04% (26 387) two, 37·09% (n = 17 468) three, 1·74% (n = 822) four, and <1% (n = 76) had more than five ARV medicine items per prescription.

Table 2. Average number of ARV prescription per patient per year according to age group

	HIV patients (N = 8999)	Average number of ARV prescriptions per patient per year[a]	Total number of ARV prescriptions (N = 47 085)	
Age band	(n)		(n)	(%[b])
Birth to 6 years	171	5·44 ± 4·28	958	2·03
Older than 6–12	230	5·69 ± 4·19	1332	2·83
Older than 12–19	76	5·06 ± 4·36	445	0·95
Older than 19–40	3033	4·94 ± 3·81	17 694	37·58
Older than 40–60	5347	5·22 ± 3·91	26 185	55·61
Older than 60 years	142	4·31 ± 3·60	470	1·00
Total	8999	5·11 ± 3·89	47 085	100

[a]Average number was calculated according to the number of ARV items claimed in each age group during 1 year.
[b]Percentage was calculated according to the total number of ARV prescriptions claimed in each age group during 1 year.

Table 3. Total number of possible DDIs identified according to the total number of ARV prescriptions per age band

Age band	Total number of ARV prescriptions *n* (%)[a]	Number of DDIs *n* (%)[b]
Birth to 6 years	958 (2·03)	18 (1·88)
Older than 6–12	1332 (2·83)	41 (4·27)
Older than 12–19	446 (0·95)	6 (0·63)
Older than 19–40	17 694 (37·58)	311 (32·40)
Older than 40–60	26 185 (55·61)	578 (60·21)
Older than 60 years	470 (1·00)	6 (0·63)
Total	47 085 (100)	960 (100)

[a]Percentage was calculated according to the total number of ARV prescriptions in each age group.
[b]Percentage was calculated according to the total number of DDIs identified in each age group.

A total of 960 DDIs were identified according to age bands of the patients. A comparison of the DDI rates against the prescription rates for each band are shown in Table 3. Patients <40 and ≤60 years presented with highest number of possible DDIs (60·21%) and prescription rates (55·61%), followed by patients ≤19 and ≤40 years with 32·40% possible DDIs and 37·58% ARV prescription rates, compared with patients older than 60 years, with the lowest possible number of DDIs (0·63%) and ARV prescription rates of 1·00%. As already stated patients in 4 and 5 age bands presented with the highest number of both patients ARV prescriptions (Tables 1 and 2).

The results of this study showed that of the possible DDIs between the ARVs in the different age bands. The most important interactions were between: IDV and RTV (20·73%; $n = 199$); EFV and LPV/RTV (6·77%; $n = 65$); and EFV and IDV (6·25%; $n = 60$) all interacting at clinical significance 2 (moderate) as shown in Table 4.

The age band with the highest number of interacting ARVs was 5 (older than 40–60 years), with the most DDIs between IDV and RTV ($n = 199$). This age band presented with the highest number of both DDIs and ARV prescriptions (Table 3). Age group 6 (older than 60 years) presented with the smallest number of DDIs and interacting ARVs. The ARVs with the most DDIs were between IDV and RTV, EFV and IDV and EFV and LPV/RTV.

DISCUSSION

A quantitative, retrospective drug utilization review was performed on ARV prescriptions claimed through a medicine claims database during 2006 to determine the prevalence of DDIs between ARV drugs in different age groups in a section of the private health care sector in South Africa.

As demonstrated in Table 1, age group 5 (older than 40–60 years) presented with the highest number of HIV patients accounting for 59·42% ($n = 53\,479$), followed by age group 4 (older than

Table 4. Number of possible interacting ARVs at moderate in the different age bands

Age band	Interacting ARVs	Prevalence
Birth to 6 years	Nelfinavir and nevirapine	5
Older than 6–12 years	Saquinavir and efavirenz	1
	Saquinavir and lopinavir/ritonavir	1
	Efavirenz and lopinavir/ritonavir	22
	Nelfinavir and nevirapine	6
Older than 12–19 years	Indinavir and ritonavir	2
Older than 19–40 years	Efavirenz and lopinavir/ritonavir	19
	Efavirenz and indinavir	60
	Efavirenz and saquinavir	2
	Indinavir and ritonavir	7
	Saquinavir and ritonavir	5
Older than 40–60 years	Efavirenz and lopinavir/ritonavir	14
	Efavirenz and nelfinavir	2
	Indinavir and ritonavir	188
Older than 60 years	Indinavir and ritonavir	2

19–40 years) with 33·70% (n = 3033). This could be explained by the fact that these two age groups are the most sexually active groups of society, and probably engaging in unprotected sex, which puts them at higher risk of HIV infection, and the most economically advantaged so could afford to visit a private health care centre. Age group 6 (61 years and older) presented with the lowest number of patients, being the less sexually active, and possibly using condoms or abstaining from sex, with the result that their chances of contracting the disease are more limited (13). According to South Africa HIV and AIDS Statistics Summary for 2006, women are more likely to be infected than men (13).

The gender distribution of the study population revealed female predominance. According to Statistics South Africa Census 2001 (14), there were more females than males in South Africa in 2001. As a limitation of the study, no demographic or clinical information of the patients was given in the database.

The results of this study showed that ARVs were prescribed to approximately 3% of all patients whose prescriptions were claimed through this medical scheme administrator in the 1-year period. ARV prescriptions accounted for 4·27% of the total number of prescriptions claimed through the database for the 1-year period.

Human immunodeficiency virus patients received an average of 5·11 ± 3·89 ARVs per prescription. Only 4·95% of the prescriptions had one ARV medicine item, 56·04% two, 37·09% three, 1·74% four and <1% had more than five. Combination therapy is recommended because combinations of ARVs create multiple obstacles to HIV replication to keep the number of offspring low and reduce the possibility of a superior mutation (15). No individual ARV drug has been demonstrated to suppress HIV infection for long. The results of this study indicated that most patients appeared to being prescribed therapy that is consistent with the recommendations, therefore complying with the standard care of using combinations of ARVs, though it is worrying that the mean number of ARV per prescription is worryingly low at much less than 3. Another limitation in this study was that no dosages of the different ARV drugs were supplied. The focus was on the principles rather than on specific interactions. It is therefore recommended that further investigations be performed on ARV dosages and their combinations to verify whether they adhere to the recommended treatment guidelines.

A total of 960 possible DDIs were identified between the ARVs with the most important DDIs between RTV and IDV (16·15%; n = 155); EFV and IDV (6·25%; n = 60); EFV and LPV/RTV (3·54%; n = 34); and SQV and LPV/RTV (2·29%; n = 22), all interacting at level 2. RTV, IDV and LPV/RTV all belong to the group of PIs and EFV to the group of NNRTIs. All currently available PIs are metabolized by the cytochrome P450 (CYP) enzyme system, and are all inhibitors of CYP3A4, ranging from weak inhibition for SQV to very potent inhibition for RTV (16). Thus in this study these were identified as the most important possible DDIs, as they are predicted to have numerous drug interactions.

Single-PI regimens significantly reduced the morbidity and mortality associated with HIV following their introduction (17). More recently, boosted PI regimens combined RTV with a second PI to achieve higher sustained levels of the second one than seen when it was given as part of a single-PI-regimen (18).

In this study, it was established that RTV combined with IDV may interact at clinical level 2. Both are PIs and according to Malaty (16), PIs also interact with each other, and these interactions are being explored for their potential therapeutic benefits. This is in line with data from Saah *et al.* (19) which suggested that higher IDV doses (800 mg) and/or RTV doses (>100 mg) might provide better efficacy, but might also contribute to greater toxicity and therefore may need dose adjustment to IDV/RTV 667/100 mg regimen.

The issue of DDIs should be a major clinical concern for all clinicians, hence the need for multiple reminders and warnings whenever more than two medicines are administered. Results of this study revealed that combining EFV with LPV/RTV may interact at clinical significance 2. It was observed in a study that the NNRTIs NVP and EFV lower plasma levels of PIs in adults and children. Therefore, it was recommended that coadministration of LPV/RTV with NVP and EFV necessitates a 30% increase in the dose of LPV/RTV in adults (20).

In another study by Aarnoutse *et al.* (21) on healthy volunteers, the effect of EFV (600 mg once daily) on the pharmacokinetics of RTV/IDV

(100 mg/800 mg twice daily) was examined resulting in decreased plasma concentrations of both IDV and RTV, on addition of EFV to RTV/IDV. The study therefore recommended that a dose of 200 mg of RTV with 800 mg of IDV can be used whenever EFV is used concomitantly, in treatment-experienced patients with more resistant virus. The above observations support the results obtained in this study that EFV, a NNRTI, and IDV, a PI, may interact at clinical significance 2 accounting for (6·25%) ($n = 60$).

Drugs commonly taken by HIV patients have a strong potential to interact with the PIs. In particular, the NNRTIs are also metabolized by CYP and have been shown to interact with PIs (16). Therefore, pharmacists and physicians must always be vigilant for drug interactions, both those that are already documented and those that are predictable from pharmacokinetic profiles, in patients receiving PIs.

More supporting evidence to the results of this study is by Moreno *et al.* (22) to verify whether RTV, a PI, could be used to prevent adverse interactions between NNRTIs and PIs, extended this strategy to concomitant EFV and IDV and their results revealed that in the absence of RTV, EFV decreased the IDV area under the concentration curve (AUC) by 31% and the C_{max} by 16%. The study therefore recommended that the IDV dose be increased from 800 to 1000 mg every 8 h.

Although HIV drug interactions are usually thought of as detrimental, resulting in a loss of therapeutic effect or toxicity, some drug interactions such as RTV boosted PI-based ARTs are beneficial and are commonly used in clinical practice (23). Therefore, pharmacists need to understand drug interaction mechanisms, remember key drug interactions, and vigilantly monitor patients for potential complications. It is also recommended that analysis on the management of the most important clinically significant DDIs between ARVs be performed.

CONCLUSION

The aim of the study was to determine the prevalence of DDIs between ARV agents in different age bands. It was established that age band 4 (older than 19–40 years) and 5 (older than 40–60 years) had the highest prevalence of possible DDIs, being the age groups with both the highest number of patients and ARV prescriptions. This knowledge will impact positively on the healthy professionals caring for HIV/AIDS patients in this age band group, in that strategies will have to sought out and interventions performed in this age band group, thus improving on HIV medical practice in South Africa.

Combination ART is a potent and effective therapy for HIV infection. Unfortunately, ARV drugs frequently interact among themselves, as well as with other anti-infectives. These interactions determine positive or negative consequences resulting in recommendations to avoid some combinations or to adjust the dosage of coadministered drugs. The effective clinical use of ARVs requires detail knowledge of interaction mechanisms by all healthcare professionals dealing with HIV/AIDS, and the consequent recommendations in their management when coadministering interacting ARVs.

ACKNOWLEDGEMENTS

The financial assistance of the South African Medical Research Council (MRC) and the South African National Research Foundation (NRF) towards the research is hereby acknowledged. Opinions expressed in this study, and conclusions arrived at, are those of the authors. Thank you to the managers of the medicines claims database that provided the data and to Mrs. M. Terblanche for assisting in proofreading the manuscript.

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ARTICLE 4:

Analysis of possible drug-drug interactions between ritonavir and other antiretroviral drugs in a private health care sector in South Africa.

2009. ***African journal of primary health care and family medicine***, 1(1): 1-6.

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Analysis of possible drug-drug interactions between ritonavir and other antiretrovirals in a section of the private health care sector in South Africa

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Keywords:
antiretroviral drugs; drug-drug interactions; human immunodeficiency virus patients; private health care; ritonavir

Dates:
Received: 02 Dec. 2008
Accepted: 10 Mar. 2009
Published: 18 June 2009

How to cite this article:
Katende-Kyenda, N.L., Lubbe, M.S., Serfontein, J.H.P., Truter, I. 2009. Analysis of possible drug-drug interactions between ritonavir and other antiretrovirals in a section of the private health care sector in South Africa. African Journal of Primary Health Care & Family Medicine, 1(1), Art. #21, 6 pages. DOI: 10.4102/phcfm.v1i1.21

This article is available at:
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ABSTRACT

Background: The introduction of human immunodeficiency virus (HIV) protease inhibitors (PIs) has led to a dramatic decline in the morbidity and mortality associated with HIV infection. However, the concomitant use of PIs and other antiretrovirals (ARVs) can be complicated by drug-drug interactions (DDIs), adversely affecting levels of PIs.

Methods: A quantitative, retrospective drug utilisation study was performed using data obtained from the medicine claims database of a pharmacy benefit management company during 2004, 2005 and 2006. The possible DDIs found among ARVS themselves were identified using the classification by Tatro.

Results: The percentage of ARV prescriptions claimed of the total number of medicine items increased from 1.68% (n = 43 482) during 2004 to 3.18% (n = 51 613) during 2005, then to 4.74% (n = 47 085) during 2006. A total of 1 326, 1 863 and 960 possible DDIs were identified among ARVs themselves for 2004, 2005 and 2006 respectively. Of these, ritonavir (unboosted or boosted) presented with the most possible DDIs, accounting for 74.28% (n = 985) for 2004; 67.90% (n = 1 265) for 2005; and 27.50% (n = 264) for 2006. The highest prevalence of DDIs identified was between ritonavir (unboosted) and saquinavir (n = 974, 5) for 2005 and 2006; followed by indinavir (n = 490, 129, 155) for 2004 to 2006; and efavirenz (n = 274) for only 2004; then ritonavir (boosted), co-formulated as lopinavir/ritonavir, and efavirenz (n = 118, 88, 34) for 2004 to 2006; nevirapine (n = 49, 37) for 2004 and 2005; indinavir (n = 9) for 2004; and saquinavir (n = 22) for 2006.

Conclusion: These findings indicate that concomitant use of PIs such as ritonavir, a potent cytochrome P450(CYP)3A4 enzyme inhibitor, and other ARVs is complicated by possible DDIs and therefore further studies need to be done on the ARV combinations and management of these DDIs.

INTRODUCTION

In managing human immunodefiency virus (HIV)-1 infection, the current best available route is to achieve both sustained suppression and altered natural history of viral replication in all cellular and body compartments, using highly active antiretroviral therapy (HAART).[1,2]

The HAART regimens currently recommended as first-line treatment are protease inhibitor (PI) based or non-nucleoside reverse transcriptase inhibitor (NNRTI) based[3]; triple nucleoside reverse transcriptase inhibitor (NRTI)-based regimens are an alternative when PI- or NNRTI-based regimens are unsuitable.[4] The clinical value of triple-combination antiretroviral (ARV) therapy has been established by a number of large randomised controlled trials showing striking improvements in disease markers, improved survival and diminished disease progression relative to single- and double-agent therapy.[5]

The introduction of HIV-1 PIs has been associated with a dramatic reduction in AIDS-related morbidity and mortality because there are potent ARV agents that, either alone or co-administered with NRTIs, have demonstrated substantial virological and immunological responses sustained over long periods of follow-up.[6] Ritonavir is one of the four potent synthetic HIV PIs that have revolutionised HIV therapy.

One of the most challenging issues encountered by providers treating patients with HIV-1 infection is the complex problem of drug-drug interactions (DDIs) associated with HAART. Guidelines for the initial treatment of HIV infection recommend the use of at least three ARVs, each of which is associated with significant DDIs. Either NNRTI-based or PI-based HAART regimens are strongly recommended. Although PIs are preferably employed, there are potent inhibitors of CYP3A4, resulting in possible DDIs that are often very complex. Among the PIs, ritonavir (a so-called booster) is the most employed in combination with other ARVs to enhance plasma drug concentration and, therefore, increase antiretroviral activity.[7] It is the most potent inhibitor of CYP3A4, therefore is the most likely PI medication to cause DDIs.[6]

A study by Boffito *et al.*[8] indicated that the use of boosted double-PI regimens can produce pharmacokinetic interactions; for example, the use of tipranavir/ritonavir with other PIs indicated a significant decrease in plasma concentrations of saquinavir, amprenavir and lopinavir. Therefore, such a combination should be avoided.

Another study performed by the same authors[8] concluded that when lopinavir/ritonavir was combined with fosamprenavir, the results showed substantially lower fosamprenavir levels than in patients dosed with fosamprenavir/ritonavir alone. As a form of managing the interaction, it was suggested that the dose of fosamprenavir be increased from 700 mg twice daily to 1 400 mg daily without changing the dose of ritonavir, though this combination could lead to a complex bidirectional interaction.[8] Once again, such a combination should be avoided in clinical practice.

The prevalence of DDIs between ritonavir and other ARVs has not been studied in the private health care sector in South Africa. Therefore, the objective of this study was to determine the prevalence of

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DDIs between ritonavir and other ARVs prescribed on the same prescription in a section of the private health care sector in South Africa for three consecutive years and suggest possible ways of managing such DDIs in clinical practice.

METHODS

Permission to conduct the study was granted by the pharmacy benefit management company and the study was approved by the Research and Ethical Committees of the North-West University, Potchefstroom Campus, and Walter Sisulu University, Mthatha Campus. This was a quantitative, retrospective drug utilisation study performed on 43 482, 51 613 and 47 087 ARV prescriptions claimed during 2004, 2005 and 2006 respectively, through the national medicine claims database of a pharmacy benefit management company in a section of the private health care sector of South Africa.

This company is an organisation that manages the benefits of a certain section of medical schemes and insurance companies in South Africa by providing a real-time auditing process to claims from pharmacies and service providers. The medical scheme administrators administered the claiming data of 80, 68 and 36 medical aid schemes during 2004, 2005 and 2006 respectively.[9] The number of medical schemes covered in 2006 was smaller as compared to 2005 and 2004, as was reflected in the smaller number of ARV prescriptions claimed. There are various pharmacy benefit management companies in South Africa and a medical scheme can decide whether a pharmacy benefit management company should manage its benefits or whether to do so independently.

The database provided information about the trade name of the drug, the National Pharmaceutical Product Interface (NAPPI) code,[1] the date the prescription was filled, the prescription number, identification numbers for the patient (dependant), physician, pharmacy and medical scheme, the number of the medicine items prescribed and the amount paid by the medical scheme. Dummy membership numbers (randomly allocated by the PBM) were used to prohibit the identification of the patient; thus maintaining anonymity. No specific patient, medical practice, pharmacy or medical scheme could be identified, thus confidentiality of information was maintained throughout the study. Data were analysed by using the Statistical Analysis System® (SAS 9.1).[10]

For the purpose of this study a drug item (medicine item) is defined according to the Medicines and Related Substances Control Act of 1965[11] as 'substance intended for use in the diagnosis, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man.' In this research the words drug items are used interchangeably with the words medicine items. In the South African context, a prescription can consist of one or more medicine (or drug) items.

The focus of this study was to determine possible DDIs between unboosted/boosted ritonavir and other ARVs, in a private health care sector in South Africa. The possible DDIs found were classified according to a clinical significance rating, and the formula for the clinical significance ratings of DDIs is described in the form of three degrees of severity, identified as major, moderate and minor.[12] Drug interactions assigned documentation levels of established, probable or suspected are considered to be well substantiated and have significance ratings of 1 (major), 2 (moderate), 3 (minor) and 4 (major/moderate). These interactions have a probability of occurring, while interactions with significance ratings 5 are not substantiated, having documentation levels of possible or unlikely.

The study population consisted of all ARV prescriptions claimed during 2004 (N = 43 482), 2005 (N = 51 613) and 2006 (N = 47 085). The data consisted of ARV drug names that were classified according to the pharmacological groups as described in the *Monthly Index of Medical Specialties* (MIMS).[13]

The data were obtained directly from the database of the pharmacy benefit management company and analysed without any direct manipulation of the data by the researcher. Certain limitations that could limit the scope of the study were identified. Data were obtained from one medicine claims database, thus limiting external validity, implying that the results can be generalised only to the specific database used as well as to the specific study population. Research was conducted from the viewpoint that all data obtained from the medicine claims database were correct and accurate.

1.The NAPPI code is a unique nine digit number implemented with electronic transactions in mind, incorporating the product name, pack size, strength and manufacturer plus exclusions.

TABLE 1
A three-year comparison of the total number of medicine items, ARV prescriptions, DDIs among ARVs and DDIs between ritonavir and other ARVs

Year	Medicine items	ARV prescriptions	DDIs among ARVs	DDIs between ritonavir (unboosted and boosted) and other ARVS
2004	2 595 254	43 482	1 326	985
2005	1 621 739	**51 613**	**1 863**	**1 265**
2006	993 804	47 085	960	264

TABLE 2
DDIs between ritonavir (unboosted) and other ARVs for 2004, 2005 and 2006

Interacting ARVs	2004		2005		2006	
	(n)	%*	(n)	%*	(n)	%*
Ritonavir + saquinavir	-	-	974	85.44	5	2.45
Ritonavir + indinavir	490	60.57	129	11.34	155	97.55
Ritonavir + efavirenz	274	33.87	-	-	-	-
Ritonavir + nevirapine	45	5.56	37	3.25	-	-
Total	**809**	**100.00**	**1 140**	**100.00**	**204**	**100.00**

*Percentage was calculated according to the total number of possible DDIs identified in a specific year

TABLE 3
DDIs between ritonavir (boosted) and other ARVs for 2004, 2005 and 2006

Interacting ARVs	2004		2005		2006	
	(n)	%*	(n)	%*	(n)	%*
LPV/RTV + efavirenz	118	67.05	88	70.40	34	98.21
LPV/RTV + nevirapine	49	27.84	37	29.60	-	-
LPV/RTV + indinavir	9	5.11	-	-	-	-
LPV/RTV + saquinavir	-	-	-	-	22	1.79
Total	**176**	**100.00**	**125**	**100.00**	**56**	**100.00**

*Percentage was calculated according to the total number of DDIs identified in a specific year.

RESULTS

The data obtained from a medicine claims database during 2004, 2005 and 2006 consisted of 2 595 254, 1 621 739 and 993 804 medicine items of which 43 482, 51 613 and 47 085 were ARV prescriptions claimed during the three years. The percentage of ARV prescriptions claimed increased from 1.68% during 2004 to 3.18% during 2005 and 4.74% during 2006. A total of 1 326, 1 863 and 960 possible DDIs were identified among ARVs themselves for 2004, 2005 and 2006 respectively. Ritonavir (unboosted and boosted) presented with the most possible DDIs, accounting for 74.28% (n = 985) for 2004; 67.90% (n = 1 265) for 2005; and 27.08% (n = 264) for 2006 (see Table 1).

As observed in Table 1, 2005 presented with the highest number of ARV prescriptions claimed from the database, giving the highest number of DDIs among ARVs themselves and also the highest number of DDIs between ritonavir (boosted and unboosted) and other ARVs. The year 2006 had fewer ARV prescriptions claimed because fewer medical aids were contracted than in 2005, and this explains the decline in DDIs both among ARVs themselves and between ritonavir and other ARVs.

As observed in Table 2, 2005 had the highest number of DDIs between ritonavir (unboosted) and other ARVs, as it was the year with the highest number of ARV prescriptions claimed from the database, followed by 2004 and 2006 respectively. The highest number of DDIs was identified between ritonavir (unboosted) and saquinavir, followed by indinavir, efavirenz and nevirapine. DDIs between ritonavir (unboosted) and saquinavir presented at clinical significance level 3 (minor),[12] with mild effects and without significantly affecting the therapeutic outcome. DDIs at clinical significance level 2 (moderate)[12] presented between ritonavir (unboosted) and indinavir, efavirenz and nevirapine – effects may cause deterioration of a patient's clinical status and additional treatment, hospitalisation or extension of stay in the hospital may be necessary.

The other regimens where most DDIs were identified were between ritonavir (boosted), co-formulated as lopinavir/ritonavir, and efavirenz (n = 118, 88, 34) for 2004 to 2006; nevirapine (n = 49, 37) for 2004 and 2005; indinavir (n = 9) for only 2004; and saquinavir (n = 22) for only 2006 (see Table 2). All ARVs were interacting at clinical significance level 2 (moderate),[12] causing deterioration of a patient's clinical status.

As observed in the Table 3, the highest number of DDIs was identified between the boosted ritonavir and efavirenz for the three years, followed by nevirapine, saquinavir and indinavir. All ARVs were interacting at clinical significance level 2 (moderate).[12]

DISCUSSION

The aim of this study was to determine the prevalence of possible DDIs between ritonavir (unboosted and boosted) and other ARVs in a section of the private health care sector, considering that HIV PIs are widely used in combination antiretroviral therapy and that certain characteristics make them prone to clinically significant DDIs with other ARVs. Data for the study were obtained from prescriptions claimed in a section of the private health care sector in South Africa. The study indicated that ARV prescriptions claimed from the database for the three years accounted for 1.92%, 3.38% and 4.73% of the total number of 2 595 254, 1 621 739 and 993 804 prescriptions claimed during 2004, 2005 and 2006 respectively. A total of 1 326, 1 863 and 960 possible DDIs were identified between ARVs themselves for 2004, 2005 and 2006 respectively. Ritonavir (unboosted and boosted) presented with the most possible DDIs, accounting for 74.28% for 2004; 67.90% for 2005; and 27.08% for 2006 (see Table 1).

The relevance of these findings for the three years is that 2004 was the year before the implementation of prescribed minimum benefits (PMBs) in HIV/AIDS in South Africa,[14] whereas 2005 was the year when PMBs in HIV/AIDS were implemented and by 2006, PMBs were fully functioning. Katende *et al.*[15] in their findings stated how the implementation of PMBs in HIV/AIDS in South Africa had a positive impact on the management of HIV/AIDS with a decrease in the number of DDIs among ARVs, as has been demonstrated in this study for the year 2006. One possible weakness of this study is that in all three years, DDIs were not identified before the patients' prescriptions were dispensed. Furthermore, there was no direct manipulation of the data by the researchers; therefore, information such as doses of interacting ARVs and dose adjustments in the different combinations was not analysed.

Since the introduction of HAART, the recommended combination therapy in treatment-naïve patients has been based on two different types of combination regimen, namely NNRTI based and PI based, having efavirenz and nevirapine as the preferred NNRTI and ritonavir (unboosted) and ritonavir (boosted) (lopinavir/ritonavir) as the preferred PI. The combination of PIs and NNRTIs is attractive because both groups of drugs have potent antiretroviral efficacy and both are not antagonistic.[16] The results of the study showed that most DDIs were between ritonavir (PI) and saquinavir (PI), nevirapine (NNRTI), efavirenz (NNRTI) and indinavir (PI) (refer to Table 3). It has been reported that PI-based regimens revolutionised the treatment of HIV infection, leading to strained viral suppression, improved immunologic function and prolonged patient survival.[17]

A randomised study done by Mathais *et al.*[18] stated that although a dose of ritonavir 600 mg twice daily is approved for antiretroviral therapy, it is poorly tolerated due to adverse gastrointestinal effects, changes in serum lipids, insulin resistance and lipoatropy. Therefore, for ritonavir to achieve the desired boosting effect, it is used in its lowest dose. It is therefore recommended that ritonavir be used to boost HIV PIs at doses of 100-200 mg once or twice daily; however, it is reported that even at these low doses, there could be adverse clinical effects, laboratory abnormalities and/or patient intolerance.[19] This demonstrates that even a change to lower doses could lead to adverse effects.

Murphy *et al.* [20] in an open-label, multicentre trial in 190 antiretroviral treatment patients compared the efficacy of lopinavir/ritonavir at doses of 800/200 mg respectively given once daily plus tenofovir and emtricitabine (both NRTIs) versus lopinavir/ritonavir 400/100 mg twice daily plus tenofovir and emtricitabine. Their results revealed that 71% of the patients treated with once-daily lopinavir/ritonavir achieved and maintained virologic suppression (VL < 50 copies/mL) as compared with 65% of the patients treated with a twice-daily dose of lopinavir/ritonavir. This study demonstrated how a once-daily dosing of lopinavir/ritonavir is therapeutically equivalent to twice-daily dosing in antiretroviral-naïve subjects.

The results of the current study show that the highest number of DDIs occurs between ritonavir and saquinavir, presenting with 979 (see Table 2). Saquinavir as the first PI to be marketed in the USA has very unfavourable pharmacokinetics because its efficacy has been very limited as a result of the low and variable plasma concentrations achieved. However, its pharmacokinetics was reported to be improved when combined with ritonavir.[6] Thus ritonavir proved to enhance the bioavailability and prolong the elimination half-life of saquinavir so that the plasma concentration time/area under the curve (AUC) of saquinavir increased as much as 30- to 50-fold in comparison with saquinavir alone.[21] Ritonavir in comparison with other PIs produces the largest increase in saquinavir plasma concentrations and thus may increase the adverse effects of saquinavir. The mechanism by which this interaction occurs is possibly decreased first-pass metabolism (CYP3A4) and post-absorbtive clearance of saquinavir. This interaction is of clinical significance and reduced dosages of saquinavir would produce satisfactory plasma concentrations if adverse effects occur. It is not clear how much ritonavir contributes to the antiviral effect of the high concentration of saquinavir because ritonavir is poorly tolerated at high doses and there are only limited pharmacokinetic data on single low doses of ritonavir and saquinavir.

In a Cochrane Review Group for HIV/AIDS, details of six randomised clinical trials[22] involving saquinavir/low-dose ritonavir (SQV/r) were retrieved. Different doses of the two drugs were administered, although 400 mg of each twice daily was the most common regimen. The results obtained revealed SQV/r 400 mg/400 mg as the most attractive option as it involved the lowest total doses of the drugs and was better tolerated than the alternatives. The WHO Guidelines[22] recommend SQV/r

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1000/100 mg twice daily. Another popular and widely studied regimen is 400 mg saquinavir + 400 mg ritonavir, and other regimens in use and under study include 1 600 mg saquinavir + 100 mg ritonavir once daily.[22]

In the current study the second highest number of DDIs occurs between ritonavir and indinavir (see Table 2). Indinavir is a potent HIV PI; however, it is also extensively and rapidly metabolised by CYP3A.[23] It is given as an 800-mg dose every eight hours; however, the regimen still results in low and variable minimum concentration values. It is therefore administered with ritonavir to improve the bioavailability and prolong the elimination half-life of indinavir, in this way to reduce the total dose necessary to achieve a potent antiretroviral plasma concentration.[24] This was reported in a study performed in 39 healthy adult volunteers, on the effect of ritonavir on the pharmacokinetics of indinavir 800 mg every eight hours; for three doses or 400- or 600-mg single doses, ritonavir increased the indinavir plasma concentrations from 21% to 110% every 12 hours.[6] However, indinavir plasma concentrations may be elevated, increasing the pharmacological and adverse effects of indinavir. This happens through possibly decreased metabolic (CYP3A4) and post-absorbtive clearance of indinavir.[16] As form of managing this interaction, it is necessary to closely monitor the patients and adjust therapy as needed.

In a randomised trial of 54 patients, Boyd *et al.*[25] compared indinavir at 800 mg three times per day versus indinavir and ritonavir at 800 mg and 100 mg respectively twice per day in 50 patients. The results revealed no differences in virological or immunologic outcome after 112 weeks of treatment of PI-naïve patients. These results demonstrated how a change in the dose frequency does not produce any change in either virological or immunological outcome. However, another study[26] of pretreated subjects receiving indinavir 800 mg and ritonavir 200 mg twice per day demonstrated HIV RNA suppression to < 400 copies/mL in 17 (58.6%) of 29 subjects at six months and in eight (57%) of 14 subjects at nine months. These results demonstrated how the same dose change results in higher rates of virologic suppression.

The results of the current study show DDIs between ritonavir, a PI, and efavirenz and nevirapine, both NNRTIs. The combination of PIs and NNRTIs has been reported to be attractive because both groups of drugs have potent antiretroviral efficacy and are not antagonistic.[16] All PIs are substrates of CYP3A4, meaning that their metabolic rate may be altered in the presence of CYP inducers or inhibitors, while NNRTIs are also substrates of CYP3A4 and can act as an inducer (nevirapine), an inhibitor (delavirdine) or a mixed inducer and inhibitor (efavirenz). Thus, these ARVs can interact with each other and others when prescribed together. When ritonavir (unboosted and boosted) is administered with nevirapine, the PI plasma levels and clinical efficacy may be reduced. Nevirapine, the prototype of NNRTI, is primarily an inducer of CYP3A4 enzymes and, therefore, would be expected to interact with the PIs. In a study, the AUC and clinical efficacy for ritonavir was reduced by 10% in the presence of nevirapine when administered to patients with HIV.[27]

In this interaction, an increase in hepatic metabolism (CYP3A4) of ritonavir is suspected. This happens through increased hepatic metabolism (CYP3A4) of the PI.[28] Therefore, as part of management careful monitoring of ritonavir plasma levels is required. The clinical response of the patient should be observed when nevirapine is started or stopped, and the dosage of ritonavir should be adjusted as needed.

Matthews *et al.*[29] in a study of indinavir-ritonavir combinations reported that regimens with ritonavir doses of > 100 mg twice per day were stopped twice as often as regimens with lower doses, primarily because of gastrointestinal intolerance. This study demonstrated how a change in dose may result in a higher rate of adverse events.

In a study[30] of 20 treatment-experienced recipients of indinavir at 800 mg twice per day plus ritonavir at 100 or 200 mg twice per day, the L90M mutation was identified in nonresponders and partial respondents but not in responders, despite more consistent through levels, as compared with standard indinavir dosing. On the contrary, another study by Campo *et al.*[31] suggested that short-term virological suppression (HIV RNA level, < 400 copies/mL) is possible for subjects with previous failure of PI-based treatment with phenotypic resistance to indinavir when treated with indinavir plus ritonavir at 800 mg and 200 mg twice per day. These results demonstrated how the same dose change can result in lower rates of resistance. Because only subtherapeutic levels of ritonavir are achieved with the use of low levels, this fosters the development of viral resistance, and as long as plasma HIV RNA levels are maximally suppressed, the development of resistance to any of the ARVs in the regimen is minimal. It is important to consider the potential for numerous clinical relevant DDIs during treatment with low-dose ritonavir-containing regimens. In this study, possible DDIs were identified between ritonavir and efavirenz. Efavirenz, another NNRTI, also induces its own metabolism. The induction of CYP3A4 by efavirenz results in enhanced metabolism of the PIs. It has been reported that efavirenz slightly but significantly increases ritonavir exposure. The effect on efavirenz pharmacokinetics has been generally found to be insignificant, although according to a report by Fiske *et al.*[32] the AUC of efavirenz increases slightly when it is combined with ritonavir. The inhibition of CYP4503A4 by ritonavir partly offsets the enzyme-inducing effects of efavirenz and nevirapine, which may otherwise advise against the combination of PIs and NNRTIs.[33] This interaction can be managed by giving 100 mg of ritonavir twice daily, thus not fully blocking the enzyme induction.

Lopinavir has a negligible bioavailability and a short half-life when used alone, but it achieves therapeutic concentrations when combined with ritonavir. In addition to the benefits of twice-daily dosing and a reduced dosage burden because of co-formulation of lopinavir and ritonavir, lopinavir plus ritonavir proved to be safe and effective.[34] The results of this study show that lopinavir/ritonavir were prescribed together with efavirenz in the three-year period, presenting possible DDIs (see Table 3). This is supported by a quantitative, retrospective drug-utilisation study in which possible DDIs were identified between lopinavr/ritonavir and efavirenz, accounting for 6.77% of DDIs.[35] Both efavirenz and lopinavir/ritonavir are inhibitors and inducers of CYP-mediated metabolism. Thus a potential DDI with efavirenz may result in an increased or decreased concentration of PIs. Management of this DDI would involve increasing the lopinavir/ritonavir dose by 33% during co-administration with efavirenz, compensating for the enzyme-inductive effect of efavirenz, resulting in reduced lopinavir levels with the standard lopinavir/ritonavir dose of 400/100 mg twice daily.[34] Despite the availability of newer agents, the wealth of clinical experience with lopinavir/ritonavir[36] ensures it a prominent place in the ARV treatment armamentarium for years to come.

CONCLUSIONS

In summary, the current standard of care for HIV patients is a triple-therapy regimen, usually consisting of two nucleoside analogues plus a PI. The availability of anti-HIV drugs facilitates many triple therapies. The PIs are extensively metabolised by the CYP 450 enzymes; therefore, drug interactions involving PIs will occur largely as a result of enzyme induction or enzyme inhibition. The results of this study show that ritonavir, a potent inhibitor of CYP3A4, presents DDIs when prescribed with other ARVs, and these can be markedly managed by dose adjustments.

LIMITATIONS OF THE STUDY

The following should be taken into consideration when evaluating these results:

Conference (Durban, South Africa). Rome: International AIDS Society; 2000.
30. O'Brien W.A., Atkinson T.L., Han X. Combination therapy with indinavir and ritonavir in antiretroviral treatment-experienced patients [abstract 2209]. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society of Microbiology; 1999.
31. Campo R., Suarez G., Miller N. Efficacy of indinavir (IDV)/ritonavir (RTV)-based regimens (IRBR) among patients with prior protease inhibitor failure [abstract]. Antiviral Therapy 2000; 5(suppl 2):27.
32. Fiske W., Benedek I.H., Joseph J.L., *et al.* Pharmacokinetics of efavirenz and ritonavir after multiple oral doses in healthy volunteers [abstract 42269]. In: Conference record of the 12th World AIDS Conference, Geneva: Marathon Multimedia; 1998:827.
33. Corbert A.H., Lim M.L., Kashuba A.D. Kaletra (lopinavir/ritonavir). Ann Pharmacothe 2003; 36:1193–1203.
34. Hsu A., Isaacson J., Brin S., *et al.* Pharmacokinetic-pharmacodynamic analysis of lopinavir/ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodefiency virus-infected patients. Antimicr Agents Chemother 2003; 47(1):350–9.
35. Katende-Kyenda N.L., Lubbe M.S., Serfontein J.H.P., Truter I. Prevalence of possible drug-drug interactions between antiretroviral agents in different age groups in a section of the private health care sector setting in South Africa. Journal of Pharmacy and Therapeutics 2008; 33:393–400.
36. Chandwan A., Shuter J. Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. Therapeutics and Clinical Risk Management 2008; 4(5):1023–33.

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ARTICLE 5:

The identification of potential drug-drug interactions between antiretroviral drugs and the usage of Prescribed Daily Doses in the evaluation of these interactions in a section of the private health care sector in South Africa.

(Accepted for publication in: *International journal of STDs & AIDS*: Date accepted 17th August 2009)

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2. Baron DN, ed. *Units, Symbols, and Abbreviations. A Guide for Medical and Scientific Editors and Authors*. 5th edn. London: Royal Society of Medicine Press, 1994

3. Medical Foundation for AIDS and Sexual Health. *Standards for NHS HIV Services*. www.medfash.org, December 2002 (last accessed 23-01-2008)

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Identification of potential drug-drug interactions between antiretroviral drugs and the usage of prescribed daily doses in the evaluation of these interactions in a section of the private health care sector in South Africa

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ABSTRACT

The aim of this study was to identify potential drug-drug interactions (DDIs) between antiretroviral (ARVs) and to determine whether Prescribed Daily Doses (PDDs) can be used in the evaluation of these interactions.

A quantitative, retrospective drug utilisation study was performed on 49995 and 81096 ARV prescriptions that were prescribed to 7664 and 10162 HIV patients for 2005 and 2006.

Potential DDIs identified in different age groups were 778 for 2005 and 1155 for 2006, of these 4.37%; 2.94% were for patients 0≤12 years, 1.03%; 0.00% for patients 12≤19 years; 69.28%; 67.97% for patients 19≤45 years; 22.49%; 23.64% for patients 45≤59 years; and 2.83%; 5.45% for patients > 59 years. The potential DDIs identified between ARVs were all interacting at clinically significant level 2 according to guidelines indicated by Tatro.[16] These results demonstrate that potential drug-drug interactions were identified between ARVs mostly in three ARV combinations containing Kaletra® (Lopinavir/Ritonavir) and Efavirenz in different PDDs and Lopinavir/Ritonavir and Nevirapine followed by two ARV combinations of Indinavir and Ritonavir; and Indinavir and Efavirenz also in different PDDs.

There is a need for more education on the prescribing protocols for ARVs in the treatment of HIV-infected patients in the private health care sector in South Africa.

INTRODUCTION

Drug-drug interactions (DDIs) account for 3% to 5% of all in-hospital medication errors and often pose serious complications when multiple medications are used. There are particular concerns in human immunodefiency virus (HIV) infected patients who are receiving highly active antiretroviral therapy (HAART).[1] Six major classes of HIV ARVs that are available for use in HAART are: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, integrase inhibitors, and chemokine receptor (CCR5) antagonists. The ARVs available in South Africa are divided into three therapeutic classes: NRTIs that include zidovudine (AZT), lamivudine (3TC), abacavir (ABC), stavudine (d4T), didanosine (DDL) and zalcitabine (ddC); NNRTIs: nevirapine (NVP) and efavirenz (EFV); and PIs: nelfinavir (NFV), indinavir (IDV), ritonavir (RTV), saquinavir (SQV) (hard gel capsule), saquinavir (soft gel capsule), amprenavir (AMV) and lopinavir (LPV).[2] The goal of using antiretroviral therapy in HIV/AIDS patients is to achieve a complete and durable suppression of plasma viral replication in order to either restore or maintain function and minimise the development of viral drug resistance.[3] The use of HAART for HIV infection has led to reduced morbidity and mortality in treated patients,[4-5] especially with the introduction of HIV-1 protease inhibitors (PIs) that have been associated with a dramatic reduction in AIDS-related morbidity and mortality.[6]

In the management of HIV-1 infection, PIs and NNRTIs are widely used in combination ARV therapy.[7] However, the use of these drugs is constrained by factors that include high pill burden, intolerable side-effects, and difficulties with long-term adherence, development of drug-resistant viral species and clinically significant drug interactions with other ARVs.[8] ARV agents possess a high potential for drug interactions, and those that involve the NNRTIs and PIs are commonly caused by the significant effects on major hepatic metabolic pathways, that include cytochrome P450 (CYP) 3A4.[9-10] The South African public sector guidelines for the use of ARV regimens in adults recommend two regimes: (1a) d4T/3TC/Efavirenz; (1b) d4T/3TC/NVP and (2) AZT/DDI/lopinavir/ritonavir (Table 1) The first-line therapy for regimen 1 for naïve adult patients consist of Stavudine (d4T) 40mg every 12 hours (or 30mg every 12 hours if <60kg) with Lamivudine (3TC) 150 mg every 12 hours, and Efavirenz (EFV) 600mg at night (or 400mg if <40kg) OR Nevirapine (NVP) 200mg daily for the first 2 weeks, increasing to 200mg every 12 hours after this.[11] According to AfA Clinical guidelines, the recommended dose for adults is 30mg 12hourly irrespective of body weight.[12]

The first-line therapy for non-naïve adults is Regimen 1a (Table 1). This regimen is for all men and women on injectable contraception and condoms. Regimen 1b (Table 1) is for women who are unable to take contraception while on therapy.[12.] The second-line therapy – regimen 2 consists of Zidovudine 300mg every

12 hours with Didanosine 400 mg once a day (250mg daily if <60kg), taken alone, dissolved in water on an empty stomach and Lopinavir/Ritonavir 400mg/100mg every 12 hours[12] as shown in Table 1.

Table 1: Recommended antiretroviral treatment regimen for adults[12]

Regimen	Drugs
Regimen 1a (First-line) For naïve adult patients	Stavudine (d4T) 40 mg every 12 hours (or 30mg every 12 hours if <60 kg) with lamivudine (3TC) 150 mg every 12 hours, and Efavirenz (EFV) 600 mg at night (or 400 mg if <40 kg) OR Nevirapine (NVP) 200 mg daily for the first 2 weeks, increasing to 200mg every 12 hours after this
For non-naïve adults (all men and women on injectable contraception and condoms)	Stavudine 40 mg every 12 hours (or 30 mg bd if <60kg) plus Lamivudine 150 mg every 12 hours plus Nevirapine 200 mg daily for 2 weeks, followed by 200 mg every 12 hours
Regimen 1b (for women who are unable to take contraception while on therapy)	Stavudine (d4T) 40 mg every 12 hours (or 30 mg every 12 hours if <60kg) plus lamivudine (3TC) 150 mg every 12 hours plus nevirapine (NVP) 200mg daily for 2 weeks, followed by 200 mg every 12 hours
Regimen 2 (Second-line)	Zidovudine (AZT) 300 mg every 12 hours with didanosine (DDL) 400 mg once a day (250 mg daily if <60 kg), taken alone, dissolved in water on an empty stomach and lopinavir/ritonavir 400 mg/100 mg every 12 hours

AZT and 3TC are listed as the initial recommendation for the dual NRTI component based on the efficacy, toxicity and clinical experience, as well as the availability of the medicines in a fixed dose combination. Other NRTIs may substitute the AZT/3TC dual NRTI component as first-line regimens. However, AZT/3TC would then be required as potential components for second-line regimens.[13] The paediatric first-line and second-line regimen are presented in Table 2.

Table 2: Recommended paediatric antiretroviral treatment regimen [12].

Regimen	Age groups	
	6 months to 3 years	>3 years old and >10kg
First-line therapy	Stavudine (d4T) Lamivudine (3TC) Lopinavir/ritonavir(LPV/RTV)	Stavudine (d4T) Lamivudine (3TC) Efavirenz (EFV)
Second-line therapy	Zidovudine (AZT) Didanosine (DDI) Nevirapine (NVP)	Zidovudine (AZT) Didanosine (DDI) Lopinavir/ritonavir (LPV/RTV)

Ease of access to HAART in the private sector, which is covered by the medical schemes, is considerably better than in the public sector. Treatment began in the form of a one-drug regimen (monotherapy), but further research indicated that a combination of three drugs was optimal. The utilisation of HAART in the public sector of South Africa is free as compared to the private sector [14]

This study evaluates DDIs between ARVs using Prescribed Daily dosages (PDDs). The PDD is the average daily amount of the drug that is actually prescribed by a specified group of prescribers for a given time period. Prescribed Daily Dosage for a drug can be determined from prescriptions and medical or pharmacy records. For drugs where the recommended dose differs from one indication to another, it is important that diagnosis is linked to the PDD. Pharmacoepidemiological information (e.g. sex, age) is also important in order to interpret a PDD.

ARV agents possess a high potential for drug interactions, and despite well-documented risks, potential DDIs between ARVs prescribed in different daily dosages have not been investigated in a private health care sector in South Africa. Therefore the aim of this study was to identify potential DDIs between ARVs and to determine to which extent PDDs can be used to manage potential DDIs between ARVs prescribed to patients in different age groups.

METHODOLOGY

A retrospective quantitative, drug utilisation study was performed on 49 995 (N = 8 506 355) and 81 096 (N = 9 029 912) ARV prescriptions prescribed to 7 664 (N = 1 218 358) and 10 162 (N = 1 259 099) HIV patients. Data were obtained from a South African Pharmacy Benefit Management company (PBM), which manages the medicines benefits of medical schemes in a section of the private health care sector of South Africa. Data were analysed for the period 1 January to 31 December 2005 and 1 January to 31 December 2006.

The database provided information about the drug's trade name, the National Pharmaceutical Product Interface (NAPPI)-code[1], the date the prescription was filled, prescription number, patient dependant-, physician-, pharmacy- and medical scheme identification numbers, the number of the medicine items prescribed, number of days supplied, patients's gender, patient's date of birth, patient's treatment date and the amount paid by the medical scheme. Dummy membership- physician-, pharmacy- numbers (randomly allocated by the PBM) were used to prohibit the identification of the patient, pharmacy and physician; thus

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1 The NAPPI-code is a unique nine digit number implemented with electronic transactions in mind; incorporating the product name, pack size, strength, and manufacturer plus exclusions.17

maintaining anonymity. The data consisted of ARV drug names which were classified according to the pharmacological groups as described in the Monthly Index of Medical Specialities (MIMS).[15]

Potential DDIs between ARVs were identified and classified according to a clinical significant rating, and the formula for the clinical significance ratings of potential DDIs are described in the form of three degrees of severity, identified as major, moderate and minor as described by Tatro.[16] Drug interactions assigned documentation levels of established, probable, or suspected are considered to be well substantiated and have significance ratings of 1, 2 or 3. These interactions have a probability of occurring, while interactions of significance ratings 4 or 5 are not substantiated – having documentation levels of possible or unlikely. This study focused on DDIs with clinical significance rating of 2 only because it is the most common between ARVs. According to Tatro significance rating of 2, the severity is moderate in which the effects may cause deterioration in a patient's clinical status. Additional treatment, hospitalisation, or an extended hospital stay may be necessary.[16]

Basic descriptive statistics, i.e., frequencies, the arithmetic mean (average), standard deviations and effect sizes (Cohen's *d*) were used to characterise the study sample, and were calculated using the Statistical Analysis System® SAS for Windows 9.1® programme.[17]

Measurement of frequency was used to indicate the total number of ARV medicine items / prescriptions claimed and the total number of patients who received ARV prescriptions during the study period and the total number of DDIs. The arithmetic mean (average), defined as the distribution of frequencies on a one-dimensional lattice,[18] was used to determine the average number of ARV medicine items per prescription and the average number of ARV prescriptions claimed per year. The standard deviation, defined as the square root of the variance,[19] was used to determine the variability in the average number of ARV medicine items per prescription and the average number of ARV prescriptions claimed per year during the study period.
Effect sizes, measured as the standardised difference between two means, [18-20] were used to determine the difference in the average number of ARV medicine items per prescription and the average number of ARV prescriptions claimed per year during the study period. Effect size can be calculated as follows:[20]

$$\text{Effect size} = d = \frac{\bar{x}_a - \bar{x}_b}{s_{\max}}$$

Practical significance of effect sizes was determined applying interpretations by Steyn.[21]

[d] = 0.2 (small effect with no practical significant difference).

[d] = 0.5 (medium effect which is observable and may be significant).

[d] = 0.8 (large effect which is significant and of practical importance).

The age groups used in this study were: Group 1: 0≤12 years; Group 2: 12≤19 years; Group 3: 19≤45 years; Group 4: 45≤59 years and Group 5: >59 years.

For the purpose of this study a drug item (medicine item) is defined according to the Medicines and Related Substances Control Act of 1965, Act 101 of 1965[22] as "substance intended for use in the diagnosis, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man." In this research the words "drug items" are used interchangeably with the words "medicine items." In the South African context, a prescription can consist of one or more medicine items (or drugs).

Permission to conduct the study was granted from the pharmacy benefit management company and approval was obtained from the Research and Ethics Committees of the North-West University, Potchefstroom campus and the Walter Sisulu University, Mthatha campus.

RESULTS

An average of 6.52 ± 4.54 ARV prescriptions (n = 49 995) per patient per year were claimed during 2005 for 7 664 patients (0.63% of the total number of patients, N = 1 218 358). During 2006, an average of 7.98 ± 4.64 ARV prescriptions (n = 81 096) per patient per year were claimed for 10 162 patients with HIV (0.81% of the total number of patients, N = 1 259 099. There was no practically significant difference in the average number of ARV prescriptions per year between 2005 and 2006. ARVs (n = 333 226) represented 0.81% of all medicine items (N = 41 333 753) and 1.66% (n = R65 301 079.00) of the total cost of all medicine items (N = R3 940 321 304.00) claimed during 2005 and 2006. The average number of ARV medicine items per prescription was 2.57 ± 0.74 during 2005, and it was 2.53 ± 0.66 during 2006, indicating no practically significant difference in the average number of medicine items per prescription for the two study years ($d<0.8$).

The results revealed that 4.49% and 4.07% of the ARV prescriptions for 2005 and 2006 respectively had one ARV item, 43.75% and 43.52% had two ARV items, 43.86% and 49.56% had three ARV medicine items, 7.82% and 2.78% had four and 0.08% and 0.06% had more than four ARV items per prescription (Table 4). Of 778 potential DDIs identified for 2005, 34.71% were for two drug items, 60.28% for three, 1.54% for four and 3.47% had more than four items. For 2006, 1155 potential DDIs were identified, of which 53.07% were for two drug items, 41.04% for three, 5.02% for four and 0.87% had more than four items. All potential DDIs were identified by guidelines according to Tatro.[16]

As demonstrated in Table 3, the highest number of ARV prescriptions consisted of triple-therapy for years 2005 and 2006. The highest number of potential DDIs was identified on prescriptions with triple-therapy for year 2005, as compared to dual-therapy for year 2006.

Table 3: Total number of ARV prescriptions and potential DDIs (level 2) according to the number of medicine items per prescription for years 2005 and 2006

No of ARV items per prescription	ARV prescriptions				Potential drug-drug interactions			
	Year 2005		Year 2006		Year 2005		Year 2006	
	(n)	%*	(n)	%*	(n)	%**	(n)	%**
1	2246	4.49	3301	4.07	-	-	-	-
2	21875	43.75	35294	43.52	270	34.71	613	53.07
3	21927	43.86	40195	49.56	469	60.28	474	41.04
4	3909	7.82	2255	2.78	12	1.54	58	5.02
5	36	0.08	51	0.06	27	3.47	10	0.87
6	2	0.00	-	-	-	-	-	-
Total	**49995**	**100.00**	**81096**	**100.00**	**778**	**100.00**	**1155**	**100.00**

*Percentage was calculated according to the total number of ARV prescriptions of a specific year.

*Percentage was calculated according to the total number of potential drug-drug interactions identified on prescriptions of a specific year.

Table 4. **Number of ARV prescriptions and potential DDIs (level 2) according to age groups for 2005 and 2006**

	Number of ARV prescriptions				Number of potential DDIs			
Age Group (yrs)	Year 2005		Year 2006		Year 2005		Year 2006	
	(n)	%*[a]	(n)	%*[a]	(n)	%*[b]	(n)	%*[b]
0≤ 12	3034	6.07	4566	5.63	34	4.37.	34	2.94
12≤19	259	0.52	550	0.68	8	1.03	0	
19≤45	35355	70.71	55397	68.31	539	69.28	785	67.97.
45≤59	10197	20.40	18716	23.08	175	22.49	273	23.64
>59	1150	2.30	1867	2.30	22	2.83	63	5.45
Total	**49995**	**100.00**	**81096**	**100.00**	**778**	**100.00**	**1155**	**100.00**

*[a]Percentage was calculated according to the total number of ARV prescriptions in different age groups of a specific year.

*[b]Percentage was calculated according to the total number of DDIs identified in different age-groups of a specific year.

As shown in Table 4, age group 3 (19≤45 years) recorded the highest number of ARV prescriptions and also the highest number of potential DDIs. This age group is the most infected age group and economically the most active of the society and could therefore afford to enter into contract with the medical schemes for their ARV treatments. There were more ARV prescriptions claimed through the medical aids for year 2006 than for 2005, and this could account for a higher number of potential DDIs for year 2006.

The total number of prescriptions with the most important potential drug-drug interactions identified between ARV combinations and their PDDs are demonstrated in Tables 5 and 6. All interactions were in clinical significance level 2 according to guidelines indicated by Tatro.[16] As observed in Tables 5 and 6 DDIs were mostly identified between combinations of lopinavir/ritonavir at PDDs 799.8mg/198mg and efavirenz 600mg, followed by indinavir 1600mg and ritonavir 200mg. Furthermore most DDIs were mostly identified in patients in age group 3(19≤45 years) followed by patients in age group 4 (45≤59 years) as will be explored in the discussion section.

Table 5: **Prescribed Daily Dose of potential interacting ARV combinations (level 2) according to age group for 2005.**

Age group (years)	Number of prescriptions	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0≤12	8	Lopinavir/Ritonavir[i]	800 mg/200 mg	Efavirenz[ii]	200 mg
	11		400 mg/100 mg		250 mg
	5		480 mg/120 mg		250 mg
	6		480 mg/120 mg		300 mg
	4	Lopinavir/Ritonavir[i]	320 mg/80 mg	Nevirapine[iii]	2600 mg
12≤19	8	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
19≤45	144	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	36		1066.4 mg/264 mg		600 mg
	2		1142.6/mg/282.9mg		600 mg
	1		533.2 mg/132 mg		300 mg
	1		3999 mg/990 mg		1200 mg
	1		4500 mg / 3999 mg		1800 mg
	2	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Nevirapine[iii]	400 mg
	17		1066.4 mg/264 mg		400 mg
	2		799.8 mg/198 mg		500 mg
	1		1066.4 mg/264 mg		500 mg
	66	Ritonavir[v]	200 mg	Efavirenz[ii]	600 mg
	14		280 mg		600 mg
	3		300 mg		600 mg
	1		300 mg		1800 mg
	1		200 mg		80 mg
	1		240 mg		600 mg
	2		600 mg		600 mg
	113	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
	8		1600 mg		280 mg
	7		1600 mg		800 mg
	3		800 mg		200 mg
	7		800 mg		280 mg
	2		1600 mg		300 mg
	1		800mg		1200 mg
	1		2400 mg		200 mg
	1		1600 mg		240 mg
	1		2400 mg		3000 mg
	2		800 mg		800 mg
	78	Indinavir[iv]	1600 mg	Efavirenz[ii]	600 mg
	4		2400 mg		600 mg
	1		2400 mg		1800 mg
	4		280 mg		600 mg
	9		800 mg		600 mg
	1		1600 mg		1200 mg
	1		1600 mg		80 mg
45≤59	59	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	16		1066.4 mg/264 mg		600 mg
	1		799.8 mg/198 mg		307 mg
	1	Lopinavir/Ritonavir[i]	1066.4 mg/264 mg	Nevirapine[iii]	500 mg
	24	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
	7		800 mg		200 mg
	2		1600 mg		280 mg
	1		2400 mg		300 mg

Table 5: Prescribed Daily Dose of potential interacting ARV combinations (level 2) according to age group for 2005.(cont)

	25	Indinavir[iv]	**1600 mg**	Efavirenz[ii]	**600 mg**
	6		**800 mg**		**600 mg**
	31	Ritonavir[v]	**200 mg**	Efavirenz[ii]	**600 mg**
	2		**280 mg**		**600 mg**
>59	**5**	Lopinavir/Ritonavir[i]	**799.8 mg/198 mg**	Efavirenz[ii]	**600 mg**
	2	Indinavir[iv]	**2400 mg**	Efavirenz[ii]	**600 mg**
	3	Lopinavir/Ritonavir[i]	**1066.4 mg/264 mg**	Nevirapine[iii]	**400 mg**
	12	Indinavir[iv]	**1600 mg**	Ritonavir[v]	**200 mg**

i Kaletra® 400 mg/100 mg/5ml; Kaletra® 80 mg/20 mg cap
ii Stocrin® 50 mg cap, 200 mg cap and 600 mg tab
iii Aspen Nevirapine®; Aspen Nevirapine® 200 mg; Cipla Nevirapine® 200 mg tab,oral susp; Viramune® 200 mg tab; Viramune oral®
iv Crixivan® 200 mg cap,400 mg cap
v Norvir® cap; Norvir® syr

Table 6: Prescribed Daily Dose of potential interacting ARV combinations (level 2) according to age group for 2006

Age group (years)	Number of prescriptions	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0≤12	6	Lopinavir/Ritonavir[i]	800 mg/200 mg	Efavirenz[ii]	200 mg
	2		400 mg/100 mg		250 mg
	1		480 mg/120 mg		200 mg
	1		480 mg/120 mg		100 mg
	2		480 mg/120 mg		250 mg
	13		480 mg/120 mg		300 mg
	3	Lopinavir/Ritonavir[i]	320 mg/80 mg	Nevirapine[iii]	2600 mg
	4		799.8 mg/198 mg		400 mg
	2	Didanosine[vi]	40 mg	Indinavir[iv]	1000 mg
19≤45	283	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	126		1066.4 mg/264 mg		600 mg
	3		533.2 mg/132 mg		600 mg
	2	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Nevirapine[iii]	1600 mg
	9		799.8 mg/198 mg		400 mg
	1		1244 mg/308 mg		400mg
	42		1066.4 mg/264 mg		400mg
	1		799.8mg / 198 mg		307mg
	107	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
	14		1600 mg		800 mg
	6		800 mg		200 mg
	3		800 mg		280 mg
	14		1600 mg		280 mg
	4		1600 mg		100 mg
	3	Indinavir[iv]	2400 mg	Efavirenz[ii]	600 mg
	8		800 mg		600 mg
	63		1600 mg		600 mg
	59	Ritonavir[v]	200 mg	Efavirenz[ii]	600 mg
	14		280 mg		600 mg
	3		600 mg		600 mg
	11	Didanosine[vi]	400 mg	Indinavir[iv]	1600 mg
	4		250 mg		1600 mg
	5		100 mg		1600 mg
45≤59	86	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	33		1066.4 mg/264 mg		600 mg
	7		1066.4 mg/264 mg		400mg
	1		266.6 mg/66 mg		600 mg
	4		799.8 mg/198 mg		400 mg
	24	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg

Table 6: Prescribed Daily Dose of potential interacting ARV combinations (level 2) according to age group for 2006 (cont)

	21		**800 mg**		**200 mg**
	5		**2400 mg**		**300 mg**
	1		**2400 mg**		**280 mg**
	23	Indinavir[iv]	**1600 mg**	Efavirenz[ii]	**600 mg**
	18		**800 mg**		**600 mg**
	31	Ritonavir[v]	**200mg**	Efavirenz[ii]	**600 mg**
	10	Didanosine[vi]	**400 mg**	Indinavir[iv]	**1600 mg**
	4		**250 mg**		**1600 mg**
	5		**100 mg**		**1600 mg**
>59	**25**	Lopinavir/Ritonavir[i]	**799.8 mg/198 mg**	Efavirenz[ii]	**600 mg**
	9		**1066.4 mg/264 mg**		**400 mg**
	1		**399.9 mg/99 mg**		**600 mg**
	2		**1066.4 mg/264 mg**		**500mg**
	17	Indinavir[iv]	**1600mg**	Ritonavir[v]	**200mg**
	9	Ritonavir[v]	**200 mg**	Efavirenz[ii]	**600 mg**

i Kaletra® 400 mg/100 mg/5ml; Kaletra® 80 mg/20 mg cap

ii Stocrin® 50 mg cap, 200 mg cap and 600 mg tab

iii Aspen Nevirapine®; Aspen Nevirapine® 200 mg; Cipla Nevirapine® 200 mg tab,oral susp; Viramune® 200 mg tab; Viramune oral®

iv Crixivan® 200 mg cap,400 mg cap

v Norvir® cap; Norvir® syr

vi Aspen®didanosine 25mg 50mg, 100mg, 150mg, Videx® 100mg chew, 150mg chew, 50mg chew, 50mg chew, 250mg EC cap, 400mg EC cap, 2mg Paed susp

DISCUSSION

This study identified potential DDIs between ARVs interacting at level 2 and determined whether PDDs can be used to manage potential DDIs between ARVs prescribed in different age groups in a section of the private health care sector in South Africa.

The results of this study showed that the highest number of potential DDIs between the ARVs was identified in triple-therapy combinations. The usual dosing of ARV drugs in the different drug combinations can result in variable and potentially toxic levels, while others having low levels are potentially inadequate to suppress the HIV virus. It has been reported that ARV therapy with three agents provides potent suppression of plasma HIV RNA levels that are below the detectable limits in the majority of treated patients, resulting in immunologic improvements, decreases in HIV-related complications, and prolonged survival.[23]

In this study, patients in age group 3 (19≤45), received the highest number of ARV prescriptions with three ARV items, as well as the highest number of potential DDIs. This is confirmed by a report in a retrospective review of ARV drug therapy, through logistic regression analysis that patients with age exceeding 42 years, with more than three comorbidities, and with treatment with three or more ARV medicine items or a PI, independently increased the risk of clinically significant drug interactions.[24] Therefore there is a need to study carefully the drug combinations to determine whether there are any potential interactions or not.

It has been demonstrated in this study that potential DDIs were identified mostly between the PIs and NNRTIs groups (Refer to Tables 5 and 6). The HIV-1 protease inhibitors are widely used in combination ARV therapy for the management of HIV-1 infection. However, certain characteristics of PIs, particularly their metabolism being mainly via the cytochrome P450 isoenzyme group and their gastric absorption being pH dependent, make them prone to clinically significant drug interactions with other ARVs.[8]

Of the PIs, ritonavir is the most potent inhibitor of CYP3A4, followed by indinavir, nelfinavir, amprenavir, and saquinavir.[8] Of the four available NNRTIs, nevirapine, a substrate and an inducer of CYP3A4, and efavirenz both an inducer and inhibitor of the CYP3A4 isoform, are also prone to potential DDIs.[25] It is important to understand potential DDIs that may occur with the use of combinations of PIs, combinations of PIs and NNRTIs, and combinations of NRTIs.

In this study, the most important interactions were identified between combinations of: Kaletra® (Lopinavir 400mg/Ritonavir 100mg) and and Stocrin® (Efavirenz 250mg) prescribed to patients in and age group

0≤12years. Efavirenz is a NNRTI, used with either PIs or NRTIs, like the PIs, EFV is extensively metabolised by the CYP450 enzymes, primarily CYP3A4, and the inhibitory activities of the PIs range from weak (saquinavir) to very potent (ritonavir).[25] Therefore, potential DDIs should be expected when EFV is coadministered with ritonavir. It has been reported that ritonavir produces a 21% increase in EFV concentration, which could be a potentially toxic level.[9,25]

The Guidelines developed by the Department of Health and Human Services (DHHS)[26] state that regimens containing EFV together with IND or LPV/RTV are not recommended because of pharmacokinetic interactions, drug toxicities, and drug resistance issues. However, according to Ian and Coffey,[27] this regimen can be prescribed but dosage adjustment is a necessity in this type of combination.

Further DDIs were identified between LPV/RTV at PDDs of 1066.4mg/264mg and EFV 600mg prescribed to patients in age group 19≤45. The doses of LPV/RTV are regarded high and could lead to potentially toxic levels. Therefore it is recommended that LPV/RTV PDDs be adjusted to LPV/RTV 400/100mg (2 tablets or 5ml) twice a day or LPV/RTV 800/200mg (4 tablets or 10ml) once daily) for ARV-naïve patients; not for patients receiving EFV, NVP, fAPV or NFV.[26]

According to DHHS treatment guidelines,[26] for regimen for ARVl-experienced patients receiving EFV or NVP, the dose of LPV/RTV is 600mg/150mg (3 oral tablets) twice daily OR LPV/RTV 533/133mg (6.7ml oral solution) twice daily with food,[26] and the recommended dosage for EFV should be 600mg daily on an empty stomach, at or before bedtime.[26]

Potential DDIs were also identified between Nevirapine (Viramune® 200mg) at PDDs of 2600mg; with LPV/RTV at PDDs of 320mg/80mg, to age group 0≤12 years; and at PDD 400mg with LPV/RTV at PDDs of 1066.4mg/264mg. as shown in Table 6. Nevirapine is an inducer of the drug – metabolising hepatic enzyme, therefore combined with ritonavir, a potent inhibitor would lead to a pharmacokinetic interaction. Therefore the PDDs at which Nevirapine was prescribed were high. The recommended daily dose for NVP is 200mg daily for 14 days; thereafter 200mg twice daily. In this study, the PDD of LPV/RTV with NVP was relatively high and this indicates a necessity for dose adjustment to NVP 200mg twice daily and LPV/RTV 400mg/100mg (2 tablets) twice daily for ARV-naïve patients, and 600mg/150mg (3 tablets) twice daily for ARV-experienced patients.[26-27]

Other drug regimens identified in this study with potential DDIs were Crixivan® (Indinavir 400mg) and Norvir® (Ritonavir 100mg) at PDDs of IND 1600mg and Ritonavir at PDD of 200mg prescribed to age group 19≤45 years; and Indinavir at PDD of 1600mg with Ritonavir at PDD of 200mg as reflected in Table 6. The

recommended dose for IND 200mg, 333mg, 400mg is 800mg every 8 hours if given unboosted. The reason for this recommended dose is because the drug has a very short half-life due to high systemic clearance.[28] The reason for the administration of RTV with IND, is that RTV improves the bioavailability of IND and prolongs its elimination half-life, and it reduces the total dose necessary to achieve a potent ARV plasma concentration. Therefore the recommended dose for a boosted IND with RTV, should be IND 800mg (400mg twice daily) and RTV 100mg or 200mg twice a day.[26] IND was given at a relatively high dose of 1600mg and 2400mg and at such levels the patient could develop nephrolithiasis,[28] therefore it is recommended that dose adjustment be done.

CONCLUSION

The results revealed the prevalence of potential drug-drug interactions on prescriptions dispensed in a section of the private health care sector of South Africa to HIV patients who are receiving HAART, particularly PI- and NNRTI-based regimens. These could complicate the management of HIV patients, since these interactions are mediated through the CYP450 system, particularly the CYP3A4 isoenzyme. It is therefore the responsibility of health care professionals, to familiarise themselves with the most common potential DDIs in the different ARV combinations, and valuable information for prescribing antiretroviral therapy.

Certain ARVs require dosage adjustments (or pharmacokinetic enhancement) when coadministered, and some combinations are contraindicated when prescribed at high doses for example LPV/RTV with EFV of IND with EFV. Therefore retrospective drug utilisation studies can be used to give information about the prescribing patterns, and PDDs adjustments can be used as a form of management of potential drug-drug interactions. It is therefore recommended that HIV guidelines be routinely revised and that health care professionals review HIV patients' medication profiles, especially as this area continues to expand and more drug interactions are discovered.

LIMITATIONS

Some limitations of this study were that there were no clinical data to do in-depth analyses of drug-drug interactions, since data were obtained directly from the medicine claims database of a medical scheme administrator in South Africa. This limited external validity of the data, implying that results can be generalised to the specific database used as well as the specific study population only. It is therefore recommended that clinical data be obtained so that PDD can be correlated with DDIs.

ACKNOWLEDGEMENTS

The financial assistance of the South African Medical Research Council (MRC) and the South African National Research Foundation (NRF) towards the research is hereby acknowledged. Opinions expressed in this paper, and conclusions arrived at, are those of the authors. Thank you to the managers of the medicines claims database that provided the data and to Mrs. M Terblanche for assisting in proofreading the manuscript.

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ARTICLE 6:

Longitudinal analysis of the prevalence of antiretroviral potential drug-drug interactions on prescriptions of general practitioners and specialists in South Africa and the evaluation of the prescribed daily doses of the interacting drugs.

(***Pharmacoepidemiology and Drug Safety:*** Submitted on 16th Oct. 2009).

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1. Emerson A, Martin RM, Tomlin M, *et al.* Prospective cohort study of adverse events monitored by hospital pharmacists. *Pharmacoepidemiol Drug Saf* 2001; 10: 85–92. DOI:10.1002/pds.574
2. Meichenbaum D and Turk D. *Facilitating Transplant Adherence: A Practitioner's Guide.* Plenum Press: New York, NY, 1987;44.
3. Cramer JA and Mattson RH. Monitoring compliance with antiepileptic drug therapy. In *Patient Compliance in Medical Practice and Clinical Trials.* Cramer JA and Spiker B (eds).Raven Press: New York, NY, 1991; 123–138.
4. FDA. Guidance for industry. Premarketing risk assessment. FDACDER/CBER, Rockville; March 2005. http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0187-gdl0002.pdf(accessed 1 January 2007).

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Longitudinal analysis of the prevalence of potential antiretroviral drug-drug interactions on prescriptions of general practitioners and specialists in South Africa and the evaluation of the prescribed daily doses of the interacting drugs.

Short title: Potential antiretroviral drug interactions

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KEYWORDS: Drug-drug interactions, antiretroviral treatment guidelines, prescribed daily doses, antiretroviral drugs, age group, adverse effects, and prescribers.

SPONSORS: No sponsors involved

CONFLICT OF INTEREST:

All the authors hereby confirm that they do not have any conflict of interest.

Abstract

Purpose:

The purpose was to determine the prevalence of potential drug-drug interactions (DDIs) between antiretroviral (ARV) drugs on prescriptions prescribed by general practitioners (GPs) and specialists (SPs) in South Africa and the evaluation of the prescribed daily doses (PDDs) of the interacting drugs.

Method:

A non-experimental, retrospective quantitative, drug utilisation study was performed on 49995, 81096 and 88988 ARV prescriptions prescribed to HIV patients from 2005 to 2007. These prescriptions were claimed through a pharmacy benefit management (PBM) company in a section of the private health care sector in South Africa. .

Results:

ARV prescriptions prescribed by GPs with potential DDIs and PDDs not according to recommended ARV dosing increased dramatically from 12.33% in 2005 to 24.26% in 2007. Those prescribed by SPs increased from 15.46% in 2005 to 35.30% in 2006 and decreased to 33.16% in 2007. The highest percentage of ARV prescriptions with potential DDIs and PDDs not according to the recommended ARV dosing guidelines were identified in ARV regimens between lopinavir/ritonavir at PDD 1066.4 mg/264 mg and efavirenz at PDD 600 mg prescribed to patients in age group (19≤45) years. These regimens were mostly prescribed by GPs as compared to SPs.

Conclusion:

There is need for more education to prescribers to be aware of the potential medication-prescribing errors associated with highly active antiretroviral therapy (HAART) which could lead to treatment failures, development of resistance and DDIs.

Introduction

The number of people living with human immunodeficiency virus (HIV) in 2007 was alarmingly large [1]. By the end of 2005, the global estimate was 38.6 million, with two thirds of those infected living in Sub-Saharan Africa with several countries in the region having adult infection rates exceeding 20% [2]. In South Africa, in 2007, about 5 million lived with the infection, which according to UNAIDS (2006), was the highest number of HIV positive people in any country, although not the highest prevalence rate [3-4].

WHO estimated in 2005, that 4.7 million people living in Sub-Saharan Africa were in urgent need of antiretroviral treatment (ART) [5]. Several initiatives to achieve large-scale delivery of ART to the infected in resource-limited countries were launched [6], with South Africa having its national, publicly funded ART programme launched in the public health care sector in 2005 [7]. In the same year Prescribed Minimum Benefits (PMBs) for HIV/AIDS was implemented in the private health care sector [8]. Despite the increased availability and affordability of ART, the proportion of HIV-positive people in South Africa who are eligible for treatment but who that are actually receiving treatment, it is low [9]. According to Johnson (2006), in the middle of 2005, an estimate of 60 000 people were receiving ART through medical schemes, workplace and community treatment programmes. By February 2006, between 80 000 and 100 000 people were receiving ART at public sector clinics [10].

Significant advances have been made in the treatment of HIV infection over the past years, and the efforts have led to the decline in morbidity and mortality associated with HIV disease [11-12]. It has been widely accepted that effective available medical technologies such as ARVs have transformed HIV/AIDS from an acute life threatening condition to an established chronic disorder within a list of other such conditions that can be effectively managed [13]. This has resulted in a shift in emphasis from preparing people to die, to preparing them to live with the virus, the drugs and the required life- style changes [14]. The use of highly active antiretroviral therapy (HAART) has resulted in delayed disease progression, improved survival, and decreased hospitalisation for patients with HIV infection.

Current guidelines for the use of ARVs recommend combinations of different ARV agents for the treatment of HIV disease, for these have led to major improvements in the management of HIV/AIDS in the developed world and increasingly in the developing world [15]. With the rapid approval of many of these agents, health care providers may not be able to familiarise themselves with these agents. This lack of knowledge can lead to an increased risk of medication errors, especially when being prescribed by non-HIV specialists [16]. Medication errors are common, harming at least 1.5 million people living in the Unites States of America (USA) every year and costing billions of dollars [17]. These errors can occur at levels of prescribing,

dispensing and/or administration, and these have been associated with prescribing errors due to inadequate knowledge of the prescriber; inadequate access to information; sound-like medication names; incorrect dosage or dose frequency; inaccurate adjustment for hepatic or renal impairment; complicated regimens; and incorrect reporting by the patient [18-19].

Despite the numerous beneficial effects of ARV therapy, new problems have emerged, such as patients' poor adherence to their regimens, virus resistance, drug interactions and drug-related adverse effects [20]. Medication-prescribing errors associated with HAART may lead to treatment failure and these errors are multifactorial including lack of knowledge about HIV treatments and complexity of regimens. Therefore clinicians caring for HIV-infected patients should be aware of the potential of prescribing errors associated with HAART and employ strategies to prevent them.

Drug-drug interaction (DDI) is an important, widely under-recognised source of medication error, representing a significant opportunity cost to health care systems [21]. Clinically significant DDIs involving ARVs are relatively common, and are reported to affect at least 14% of 342 patients in the USA [22] and 23% to 26% of 220 HIV-infected outpatients in the Netherlands [23]. Since DDIs determine positive and negative consequences to HIV-infected patients, recommendations to avoid some combinations or to adjust the dosage of co-administered drugs were formulated. Guidelines for the use of ARVs in adults and adolescents infected with HIV-1 were developed by a Department of Health and Human Services (DHHS) expert panel and provide guidance to clinicians on when to initiate ARV treatment, preferred and alternative treatment choices and goals, the use of ARVs in special population groups, and management of the treatment-experienced patients. These guidelines also provide information on standard dosing for ARVs, dose adjustments for patients with other complications like renal and hepatic impairment, adverse effects, and DDIs [24]. The South African public sector ART guidelines for adults recommend two regimens [25-26], as shown in Table 1. The recommended regimen in children is shown in Table 2 [27].

Table 1: Recommended ART regimens in adults [25-26]

Regimen	Drugs
1a	Stavudine (d4T) 40 mg every 12 hours (or 30 mg every 12 hours if < 60 kg) plus lamivudine (3TC) 150 mg every 12 hours plus efavirenz (EFV) 600 mg0 mg at night (or 400 mg if < 40 kg).
1b	d4T 40 mg every 12 hours (or 30 mg twice daily if <60 kg) plus 3TC 150 mg every 12 hours plus nevirapine (NVP) 20 daily for the first 2 weeks, followed by 20 mg every 12 hours.
2	Zidovudine (AZT) 300 mg every 12 hours with didanosine (ddI) 40 mg once a day (250

	mg daily if <60 kg), taken alone, dissolved in water on an empty stomach and lopinavir/ritonavir (LPV/r) 400/200 mg every 12 hours

Table 2: Recommended regimen in children [27]

Paediatric first – line therapy – Regimen 1		
	6 months – 3 years	>3 years old and > 10 kg
First-line	stavudine (d4T) lamivudine (3TC) lopinavir/ritonavir (LPV/r)	stavudine (d4T) lamivudine (3TC) efavirenz (EFV)
Paediatric second – line therapy – Regimen 2		
	6 months – 3 years	>3years old and > 10 kg
First-line	zidovudine (AZT) ddI nevirapine (NVP)	zidovudine ddl lopinavir/ritonavir (LPV/r)

For first-line therapy (regimen 1), paediatric dosages are given per body surface area. For second-line therapy (regimen 2), the ART dosages are prescribed according to body weight. Efavirenz is given if age > 3 years, and nevirapine if < 3 years [27].

One set of the South African private sector guidelines for starting ART in adults recommended the following:

- The patient must be ready for treatment and the patient should have a WHO stage 4 condition or other serious morbidity; or
- Two CD4 counts lower than 350 done at least six weeks apart [28].

In the public sector the patient selection criteria for indication of ART include the following:

- CD4 count < 200 cells/mm^3 irrespective of WHO stage or WHO Stage IV disease irrespective of CD4 count.
- Patient expresses willingness and readiness to take ART adherently [25]. The recommended drug combinations are shown in Table 3.

Table 3: Recommended drug combinations in the private sector [28]

Protease Inhibitors (PIs)	Dose for Protease Inhibitor (PI)– naïve		Dose for Protease inhibitor (PI)-experienced	
	Nevirapine	Efavirenz	Nevirapine	Efavirenz
Atazanavir/ritonavir	Not recommended	400 mg/100 mg once a day	Not recommended	400 mg /100 mg
Darunavir/ritonavir	Standard dose	Standard dose	Standard dose	Standard dose
Lopinavir/ritonavir	Standard dose	Standard dose	600 mg/150 mg twice daily	600 mg/150 mg
Saquinavir/ritonavir	Standard dose	Standard dose	Standard dose	Standard dose

Certain disease management programmes in the South African private sector uses the initiation criteria for ART in a child that as shown in Table 4.

Table 4: CD4 criteria for initiation of ART in the private sector [28].

Age	< 12 months	12 months to 35 months	36 months to 59 months	5 years and over
CD4	All	< 20	< 20	< 15
Absolute CD4 count		< 750	< 500	< 350

The recommendations on which to start ART in children are as follows:

For Infants: either 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) + 1 Protease Inhibitor (PI) (lopinavir/ritonavir) or 2 (NRTI) + 1 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (nevirapine) (Not to be used if mother or infant received single-dose nevirapine as part of the strategy to prevent mother-to-child transmission).

For Children: either 2 NRTI + PI (lopinavir/ritonavir) or NRTI + NNRTI (efavirenz or nevirapine) [28].

The influence of the prescriber on the prevalence of potential DDIs between ARVs in different regimens has not been studied in the private sector in South Africa.. Therefore the aim of this study was to investigate the prevalence of potential DDIs between ARVs on prescriptions prescribed by general practitioners and specialists to HIV patients in different age groups and the evaluation of the PDDs of the interacting drugs.

METHODS

A non-experimental, retrospective quantitative, drug utilisation study was performed on 49 995 (N = 8 506 355), 81 096 (N = 9 029 912) and 88 988 (N = 8 015 538) ARV prescriptions prescribed to 7 664 (N = 1 218 358), 10 162 (N = 1 259 099) and 10 061 (N = 911 212) HIV patients. Data were obtained from a South African PBM company, which manages the medicines benefits of medical schemes in a section of the private health care sector of South Africa. Data were selected for three years from 1 January 2005 to 31 December 2007. During 2008, this PBM managed the beneficiaries' medicine benefits on behalf of 38 schemes. Each South African Community Pharmacy and 98% of dispensing doctors were on the PBM service provider database [29].

The following information was obtained from the database: drug's trade name, National Pharmaceutical Product Interface (NAPPI)-code [30], date of refilling the prescription, prescription number, patients' dependant-, physician-, pharmacy- and medical scheme identification numbers, number of the medicine items prescribed, number of days supplied, patients' gender, patients' date of birth, patients' treatment date (dispeinsing date) and the amount paid by the medical scheme. Dummy membership-, physician-, pharmacy-numbers (randomly allocated by the PBM) were used to prohibit the identification of the patient, pharmacy and physician; thus maintaining anonymity. ARV drug names were classified according to the pharmacological groups as described in the Monthly Index of Medical Specialities (MIMS) [30].

Prescribers of ARV prescriptions were divided into the following categories:

- General medical practitioners: This group includes all the medical providers that are registered with the Health Professions Council of South Africa (HPCSA) as a general medical practitioner (GP).
- Prescribers from the following specialist (SP) areas which include *inter alia* the following prescribers: Anaesthesiology, cardiology, paediatrics, clinical haematology, dermatology, gastroenterology, neurology, obstetrics and gynaecology, and so on.

Potential DDIs between ARVs were identified and classified according to a clinical significant rating. The formula for the clinical significance ratings of potential DDIs were described in three degrees of severity, identified as major, moderate and minor as described by Tatro [31]. Drug interactions assigned documentation levels of established, probable, or suspected were considered to be well substantiated and to have significance ratings of 1, 2 or 3. These interactions were considered to have a probability of occurring, while interactions of significance ratings 4 or 5 were considered as not substantiated – having documentation levels of possible or unlikely. This study focused only on DDIs with clinical significance rating of 2 because they were the most common interactions between ARVs. According to the clinical guidelines of Tatro [31], clinical significance 2 can be considered to have a moderate severity, in which the effects may cause

deterioration in a patient's clinical status. Therefore additional treatment, hospitalisation or an extended hospital stay may be necessary.

The study evaluated potential DDIs between ARVs by using PDDs. According to the World Health Organization (WHO), a PDD is defined as "*the average dose prescribed according to a representative sample of prescriptions.*"[32]. It is of great importance that the PDD be related to the diagnosis made for the prescribed medication. The PDD of a drug can be calculated by multiplying the number of tablets (or volume of suspension or syrup) dispensed during the treatment period and the strength per tablet (or per ml), divided by the days supplied [33]. In this study, the reference guides used to evaluate PDDs were according to the recommended ARV dosing [25-28].

Basic descriptive statistics, i.e., frequencies, the arithmetic mean (average), standard deviations and effect sizes (Cohen's *d*) were used to characterise the study sample, and were calculated using the computer software Statistical Analysis System® SAS for Windows 9.1® [34].

Measurement of frequency was used to indicate the total number of ARV prescriptions claimed and the total number of patients who received ARV prescriptions and the total number of DDI. The arithmetic mean (average), defined as the distribution of frequencies on a one-dimensional lattice [35], was used to determine the average number of ARV medicine items per prescription and the average number of ARV prescriptions claimed per year. The standard deviation, defined as the square root of the variance [35], was used to determine the variability in the average number of ARV medicine items per prescription and the average number of ARV prescriptions claimed per year during the study period.

Effect sizes, measured as the standardised difference between two means [35-37], were used to determine the difference in the average number of ARV medicine items per prescription and the average number of ARV prescriptions claimed per year during the study period. Effect size can be calculated as follows [37]:

$$\text{Effect size} = d = \frac{\overline{x}_a - \overline{x}_b}{s_{\max}}$$

Practical significance of effect sizes was determined applying interpretations by Steyn [38].

[d] = 0.2 (small effect with no practical significant difference).

[d] = 0.5 (medium effect which is observable and may be significant).

[d] = 0.8 (large effect which is significant and of practical importance).

The age groups used in this study were: Group 1: 0≤12 years; Group 2: 12≤19 years; Group 3: 19≤45 years; Group 4: 45≤59 years and Group 5: >59 years.

For the purpose of this study a drug item (medicine item) is defined according to the Medicines and Related Substances Control Act of 1965, Act 101 of 1965 as amended [38] as "substance intended for use in the diagnosis, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man." In this research the words "drug items" are used interchangeably with the words "medicine items." In the South African context, a prescription can consist of one or more medicine items (or drugs).

Permission to conduct the study was granted fby the PBM Company and approval was obtained from the Research and Ethics Committees of the North-West University, Potchefstroom campus, (ethical number 07M01) and the Walter Sisulu University, Mthatha campus.

RESULTS

ARV prescriptions represented 0.59% (n = 49 995) of all prescriptions claimed during 2005 (N = 8 506 355), 0.90% (n = 81 096) of all prescriptions (N = 9 029 912) claimed during 2006 and 1.11% (n = 88 988) of all prescriptions (N = 8 015 535) claimed for 2007. It was observed that in the three years, GPs prescribed more ARV prescriptions than SPs and these increased from 2005 to 2007. The highest percentage of ARV prescriptions for both GPs and SPs was for prescriptions with three ARV items, followed by two ARV items. (see Table 5). No practical significant difference were found between the average number of ARV medicine items per prescription ($d < 0.8$) claimed per year for the different years.

Table 5: Number of ARV prescriptions according to the number of ARV items per prescription and prescriber for three years.

Number of ARV items per prescriptions per year (%*)						
No of ARV items per prescription	**Year 2005**		**Year 2006**		**Year 2007**	
	GPs N = 45954	**SPs N = 4041**	**GPs N = 74318**	**SPs N = 6778**	**GPs N = 80908**	**SPs N = 8080**
1	1673 (3.64%)	573 (14.18%)	2523 (3.39%)	778 (11.48%)	2078 (2.56%)	584 (7.23%)
2	1992 (43.35)	1952 (48.31%)	32083 (43.17%)	3211 (47.37%)	44876 (55.47%)	4693 (58.08%)
3	20635 (44.91%)	1292 (31.97%)	37715 (50.75%)	2480 (36.59%)	32356 (39.99%)	2439 (30.19%)
4	3692 (8.03%)	217 (5.37%)	1952 (2.63%)	303 (4.47%)	1550 (1.92%)	352 (4.35%)
5	30 (0.07%)	6 (0.15%)	45 (0.06%)	6 (0.09%)	47 (0.06%)	12 (0.15%)
6	1 (0.00%)	1 (0.02%)	0 (0.00%)	0 0.00	1 (0.00%)	0 (0.00%)

**Percentage was calculated according to the total number of ARV prescriptions claimed for the specific year.*

GPs: General Practitioners; SPs: Specialists; ARV: Antiretroviral

The total number of ARV prescriptions according to different age groups and different prescribers is shown in Table 6.

Table 6: Number of ARV prescriptions according to prescriber for the different age groups for three years.

Age Group (Years)	Year 2005		Year 2006		Year 2007	
	GPs N=45954	SPs N=4041	GPs N=74318	SPs N=6778	GPs N=80908	SPs N=8080
0≤12	2662 (5.79%)	372 (9.21%)	3914 (5.27%)	652 (9.62%)	4003 (4.95%)	741 (9.17%)
12≤19	2334 (0.51%)	26 (0.64%)	491 (0.66%)	59 (0.87%)	707 (0.87%)	88 (1.09%)
19≤45	32471 (70.66%)	2884 (71.37%)	51188 (68.87%)	4209 (62.10%)	54391 (67.23%)	4792 (59.31%)
45≤59	9551 (20.78%)	646 (15.91%)	17100 (23.01%)	1616 (23.84%)	19914 (24.61%)	2149 (26.59%)
>59	1037 (2.26%)	113 (2.80%)	1625 (2.19%)	242 (3.57%)	1893 (2.34%)	310 (3.84%)

**Percentage was calculated according to the total number of ARV prescriptions according to prescriber for the specific year.*

Table 7: Number of ARV prescriptions with potential DDIs (level 2) according to age groups and prescriber per year

Age group (years)	Year 2005		Year 2006		Year 2007	
	GPs N = 681	SPs N = 97	GPs N= 976	SPs N = 179	GPs N = 981	SPs N = 196
0≤12	23 (3.38%)	11 (11.34%)	27 (2.77%)	7 (3.91%)	17 (1.73%)	13 (6.63%)
12≤19	8 (1.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (0.51%)	0 (0.00%)
19≤45	467 (68.58%)	72 (74.23%)	648 (66.39%)	137 (76.53%)	664 (67.68%)	151 77.04%)
45≤59	165 (24.23%)	10 (10.31%)	249 (25.51%)	24 (13.41%)	225 (22.94%)	26 (13.27%)
>59	18 (2.64%)	4 (4.12%)	52 (5.33%)	11 (6.15%)	70 (7.14%)	6 (3.06%)

**Percentage was calculated according to the total number of ARV prescriptions with potential DDIs according to prescriber*

The results in Table 7 reveal that the percentage of prescriptions with potential DDIs (level 2) stayed approximately the same during the three years with 1.6% (N = 49 995), 1.4% (N = 81 096) and 1.3% (N = 88 988) of ARV prescriptions for 2005, 2006 and 2007 respectively.

The total number of potential DDIs (level 2) identified between ARVs according to prescriber and age group is shown in Table 7. Of the total number of potential DDIs (N= 778) identified between ARVs prescribed in 2005, 87.53% were prescribed by GPs and 12.47% by SPs. For year 2006, the total number of potential DDIs identified between ARVs were 1155, of which, 84.50% were prescribed by GPs and 15.50% by SPs. In 2007, of the total number of potential DDIs (N = 1117) identified between ARVs, 83.35% were prescribed by GPs and 16.65% prescribed by SPs. As observed in the three years, most potential DDIs were identified in GP prescriptions to patients in age group (19≤45 years) followed by age group (45≤59 years).

Potential DDIs identified between ARV drug regimens that were prescribed by GPs and SPs with PDDs not according to the recommended ARVs dosing according to patients' age for the three years of study are shown in Tables 8 to 10. Of the total number of ARV prescriptions (N = 778) with potential DDI claimed during 2005, 12.72% (n = 99) were prescriptions in ARV combinations with PDDs that were not according to the recommended ARV dosing [25-26] for the different age groups. In 2006 the total number of ARV

prescriptions (N = 1155) with potential DDI in ARV combinations with PDD that were not according to the recommended ARVs dosing [24-25] increased dramatically to 21.29% (n = 246). The same trend was experienced during 2007. From the 1177 ARV prescriptions with potential DDI claimed during 2007, 303 (25.74%) were ARV combinations with PDDs that were not according to the recommended ARV dosing [25-26].

For 2005 a higher percentage (15.46%) of ARV prescriptions with potential DDI prescribed by SPs (N = 97) had PDDs not according to the recommended ARV dosing than those prescribed by GPs (12.33%, N = 681). For year 2006, of the total number of ARV prescriptions with potential DDIs (N = 1155), prescribed by GPs, 183 (18.75%) prescriptions had PDDs not according to the recommended ARV dosing. A much higher percentage (35.20%, n = 65) of ARV prescriptions with potential DDIs prescribed by SPs (N = 179) had PDDs not according to the recommended ARV dosing. While for year 2007, of the total number of ARV prescriptions with potential DDIs prescribed by GPs (N = 981) with incorrect PDDs accounted for 24.26% (n = 238) as compared to higher prevalence of 33.16% 9 (n = 65) of ARV prescriptions with DDI prescribed by SPs (N = 196).

It should also be noted that from the results in Tables 8 to 10 for the three years, the highest numbers of incorrect PDDs with DDI were identified in ARV combinations of lopinavir/ritonavir at PDD 1066.4 mg / 264 mg with efavirenz at PDD 600 mg; nevirapine at PDD 400 mg. Then indinavir 1600 mg with ritonavir 800 mg; ritonavir 600 mg with efavirenz 600 mg; saquinavir 800 mg with efavirenz 800 mg for both GPs and SPs with the highest number of prescriptions prescribed by GPs to patients in age group (19≤45 years) followed by patients in age group (45≤59 years). The highest number of ARV prescriptions with potential DDIs and PDDs prescribed not according to recommended ARV dosing were prescribed to patients in age group (19≤45 years) accounting for 67.68% (n = 67) for 2005; 76.42% (n = 246) for 2006 and 73.93% (n = 224) for 2007.

Table 8: Number of ARV prescriptions with DDIs prescribed not according to the recommended ARV dosing and age group for 2005.

GENERAL PRACTITIONERS					
Age group (years)	Number of prescriptions (N =681)	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0≤12	**8**	Lopinavir/Ritonavir	**800 mg/200 mg**	Efavirenz	**200 mg**
	4	Lopinavir/Ritonavir	**320 mg/80 mg**	Nevirapine	**2600 mg**
19≤45	**30**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	1		**4500 mg/3999 mg**		**1800 mg**
	15	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
	1		**1066.4 mg/264 mg**		**500 mg**
	1	Ritonavir	**300 mg**	Efavirenz	**1800 mg**
	1	Indinavir	**2400 mg**	Ritonavir	**3000 mg**
	2		**800 mg**		**800 mg**
	1	Indinavir	**2400 mg**	Efavirenz	**1800 mg**
45≤59	**16**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	1	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**500 mg**
>59	**3**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
Total	84				
SPECIALISTS					
Age group (years)	Number of prescriptions (N = 97)	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
19≤45	**6**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	2		**1142.6 mg/282 mg**		**600 mg**
	1		**3999 mg/990 mg**		**1200 mg**
	2	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
	2		**799.8 mg/198 mg**		**500 mg**
	1	Indinavir	**800 mg**	Ritonavir	**1200 mg**
	1	Indinavir	**1600 mg**	Efavirenz	**1200 mg**
Total	15				

Table 9: Number of ARV prescriptions with DDIs prescribed not according to the recommended ARV dosing and age group for 2006.

GENERAL PRACTITIONERS					
Age group (years)	Number of prescriptions (N = 976)	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0≤12	**6**	Lopinavir/Ritonavir	**800 mg/200 mg**	Efavirenz	**200 mg**
	3	Lopinavir/Ritonavir	**320 mg/80 mg**	Nevirapine	**2600 mg**
19≤45	**101**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	26	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
	1		**1244 mg/308 mg**		**400 mg**
	2		**799.8 mg/198 mg**		**1600 mg**
	14	Indinavir	**1600 mg**	Ritonavir	**800 mg**
	3	Ritonavir	**600 mg**	Efavirenz	**600 mg**
45≤59	**11**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	7	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**400 mg**
>59	**9**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**400 mg**
	2	Lopinavir/Ritonavir	**1066.4 mg/264 mg**		**500 mg**
Total	183				
SPECIALISTS					
Age group (years)	Number of prescriptions (N = 179)	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
19≤45	**25**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	16	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
45≤45	**22**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
Total	63				

Table 10: Number of ARVprescriptions with DDIs prescribed not according to the recommended ARV dosing and age group for 2007.

GENERAL PRACTITIONERS					
Age group (years)	Number of prescriptions (N = 981)	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0≤12	**9**	Lopinavir/Ritonavir	**640 mg/160 mg**	Efavirenz	**350 mg**
	6	Lopinavir/Ritonavir	**799.8 mg/198 mg**		**200 mg**
19≤45	**145**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	3	Lopinavir/Ritonavir	**1599.6 mg/264 mg**	Efavirenz	**600 mg**
	8	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
	9	Lopinavir/Ritonavir	**799.8 mg/198 mg**		**500 mg**
	2	Indinavir	**1600 mg**	Ritonavir	**800 mg**
	18	Saquinavir	**800 mg**	Efavirenz	**800 mg**
45≤59	**17**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	13	Saquinavir	**800 mg**	Ritonavir	**800 mg**
>59	**8**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**500 mg**
Total	238				
SPECIALISTS					
Age group (years)	Number of prescriptions (N = 196)	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
19≤45	**23**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	16	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
45≤45	**22**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	3	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
>59	**1**	Lopinavir/Ritonavir	**3999.9 mg/990 mg**	Efavirenz	**600 mg**
Total	65				

DISCUSSION

The aim of the study was to determine potential ARV DDIs and to evaluate PDDs of interacting drugs with specific reference to prescriber and age group in a section of a private health care sector in South Africa.

From the results it is evident that the percentage of ARV prescriptions that were claimed through the PBM increased from year 2005 to 2007. These results are supported by the WHO/UNAIDS press release in 2006 that the number of HIV-infected individuals receiving treatment in Sub-Saharan Africa was steadily increasing [40]. It was also observed that most of the ARV prescriptions by GPs and SPs had two and three ARV items as shown in Table 1. This is supported by the fact that combination ARV regimens especially those containing HIV type 1 protease inhibitors provide clinical benefits and can achieve long-term virus suppression [2]. Furthermore it was stated that the clinical value of triple combination ART has been established by a number of large randomised controlled trials showing striking improvements in disease markers (e.g. viral load, CD4 cell count) and improved survival and diminished disease progression relative to single- and double-agent therapy [8,41-42]. According to Aid for AIDS clinical guidelines, monotherapy is not recommended; it should only be used for prophylaxis [28].

It was also noted that patients in age group (19≤45 years) in all three years presented the highest number of ARV prescriptions followed by patients in age group (45≤49 years) (see Table 2).. A study performed in rural South Africa, in KwaZulu-Natal, the province with South Africa's highest HIV prevalence [43], also confirmed that the prevalence of HIV in adults (15-54 years) had reached 23% in 2003/2004, with 27% of resident women (15-49 years) and 14% of resident men (15-54 years).

Drug-drug interactions between ARVs interacting at level 2 (moderate) were identified according to prescribers and age groups. As shown in Table 7, percentage of ARV prescriptions with potential DDIs (level 2) stayed approximately the same during the three years studied between 1.6% (2005) and 1.3% (2007) of ARV prescriptions. Most of the ARV prescriptions with DDIs were prescribed for the three years by GPs with 87.53%, 84.50% and 83.35% as compared to 12.47%, 15.50% and 16.65% for DDIs identified in ARV prescriptions prescribed by SPs. This can be explained by the fact that most of the ARV prescriptions prescribed during the three years were prescribed by GPs (Table 6 and Table 7). However, the percentage of ARV prescriptions with potential DDIs prescribed by GPs decreased from 87.53% to 83.35% and those prescribed by SPs increased from 12.47% to 16.65% for the study years 2005 to 2007.

Drug interactions are of particular concern in patients infected with HIV who are receiving HAART [10]. Though the combination of ARV treatment is a potent and effective therapy for HIV infection, unfortunately, ARV drugs frequently interact among themselves because many of them are metabolised through the CYP450 systems, with CYP3A4, CYP2D, and CYP2C9/19 the primary isoenzymes involved in the drugs' metabolism [8, 44]. These interactions determine positive or negative consequences resulting in recommendations to avoid some combinations or to adjust the dosage of coadministered drugs.

After identification of DDIs between ARVs in different regimens, further investigation was done to determine those ARV regimens with DDIs containing PDDs that were not according to the recommended ARV dosing and results obtained are shown in Tables 8 to 10. Although the percentage of ARV prescriptions with potential DDIs (level 2) stayed approximately the same, the prevalence of those ARV prescriptions with DDIs where the prescriptions had ARV combinations with PDDs not according to the recommended ARV dosing [25-26] for the different age group increased from 12.72% in 2005 to 25.74%. Further analysis indicated that the prevalence of ARV prescriptions with potential DDIs and PDDs not according to the recommended ARV dosing prescribed by GPs increased dramatically from 12.33% in 2005 to 24.26% in 2007 of ARV prescriptions with DDIs prescribed by GPs. Those prescribed by SPs increased from 15.46% in 2005 to 35.30% in 2006 and decreased to 33.16% in 2007.

It is noted that ARV regimens most identified with PDDs not according to the recommended ARV dosing were between lopinavir/ritonavir (PI) and efavirenz (NNRTI), lopinavir/ritonavir (PI) with nevirapine (NNRTI), Ritonavir (PI) with efavirenz (NNRTI), indinavir (PI) with ritonavir (PI), saquinavir (PI) with efavirenz (PI) and saquinavir (PI) with ritonavir (PI).

As observed in Tables 8 to 10, the most commonly prescribed ARV drug with DDIs is coformulated lopinavir/ritonavir. This was the first and only coformulated HIV-1 protease inhibitor. It was reported in a review that large clinical trials have demonstrated lopinavir/ritonavir's clinical efficacy in both antiretroviral-naïve and –experienced patients [44]. The immunologic and virologic benefits of treatment with this agent have been proved in HIV-infected adults, adolescents and children [45].

Results obtained for the three years of study for both GPs and SPs prescribing ARV regimens with DDIs prescribed not according to the recommended ARV dosing are shown in Tables 8 to 10. As observed in the tables, GPs prescribed lopinavir/ritonavir for patients (0≤12 years). One of the limitations of this study was that the weights of the patients particularly for children were not available; therefore it was not clear at what patients' weight and specific age this coformulation was prescribed. Otherwise the safety, efficacy, and pharmacokinetic profiles of lopinavir/ritonavir in paediatric patients below the age of 6 months have not been established. It was assumed that patients were older than 6 months who received 14 prescriptions for lopinavir/ritonavir (LPV/r) 800 mg/200 mg and efavirenz (EFV) 200 mg; LPV/r 320 mg/80 mg and nevirapine 2600 mg (n = 7) and LPV/r 640 mg/160 mg; 799.8 mg/198 mg with EFV 350 mg; 200 mg respectively (n = 15). According to the treatment guidelines for the management of HIV-infected children, formulated by the National Department of Health South Africa 2005 [27], the recommended paediatric dose for LPV/r is <15 kg + 12 mg lopinavir/kg and ≥15 kg = 10 mg lopinavir/kg twice daily. In this case lopinavir/ritonavir was prescribed in a higher PDD considering one capsule of lopinavir/ritonavir to be 133.3 mg/33.3 mg, and the maximum dose should be 3 capsules (399.9 mg/99.9 mg) [26].

According to Chandwani in the review on lopinavir/ritonavir in the treatment of HIV-1 infection, the recommended dosage of lopinavir/ritonavir in children is 100 mg/25 mg twice daily to 400 mg/100 mg, based upon the body surface area or weight of the child [45]. Therefore if given in PDDs greater than the recommended dosages, the patient will experience side-effects like diarrhea, nausea and vomiting, and metabolic derangements, including hyperlipidemia and glucose intolerance [45].

In this study nevirapine was also prescribed in a higher dose of 2600 mg to patients (0≤12 years) for years 2005 and 2006. The recommended pediatric dose for nevirapine is 10 mg/ml or 200 mg tablet as an initial dose and 4 mg/kg once daily for 14 days. If no rash develops, it is followed by a maintenance dose of 7

mg/kg twice daily for children <8 years old, or 4 mg/kg twice daily for children >8 years old [27]. Therefore at such a high dose, the patient may experience adverse effects like rash including Stevens - Johnson syndrome, symptomatic hepatitis, including fatal hepatic necrosis [27].

Results from this study demonstrated that GPs prescribed lopinavir/ritonavir at PDDs 1066.4 mg/264 mg; 4500 mg/3999 mg; 1599.6 mg/264 mg to patients 19≤45 years for the three years studied. The standard adult dose of lopinavir/ritonavir is 400 mg/100 mg (2 tablets or 5 ml) twice daily or lopinavir/ritonavir 800/200 mg (4 tablets or 10ml) once daily [26]. Therefore in this study it was given at higher PDDs. Another limitation of this study was that information about HIV-naïve or –experienced patients was not available from the database. Otherwise once-daily dosing for lopinavir/ritonavir is only recommended for treatment-naïve patients, not for patients receiving efavirenz, nevirapine or nelfinavir. When lopinavir/ritonavir is given with efavirenz or nevirapine, the recommended dose for treatment-experienced patients is 600 mg/150 mg (3 oral tablets twice daily or 533 mg/133 mg) (6.7ml oral solution) twice daily with food [26-27, 44].

The effectiveness of twice daily doses of lopinavir/ritonavir with efavirenz was confirmed in a randomised non-blinded study [47]. The study compared combination therapy with lopinavir/ritonavir 533 mg/133 mg twice daily and efavirenz once daily (in an NRTI-sparing regimen) with efavirenz and two NRTIs in patients (n = 236) who switched from PI or NNRTI-based regimens. The results showed that the combination of two NRTI with efavirenz was more effective in achieving virologic suppression. The lopinavir/ritonavir-based regimen in the study had significantly more toxicity-related discontinuations and shorter time to virologic failure ($p = 0.001$) [47]. The most frequent adverse effects reported with lopinavir/ritonavir in adults were diarrhea, nausea, and vomiting [48]. It was reported that 15% to 25% of the patients experienced diarrhea which was dose-related, occurring more frequently with lopinavir/ritonavir 800/200 mg once daily dose than 400 mg/100 mg twice-daily daily dose [48].

Results from the study revealed that other ARV regimens where DDIs were identified and containing PDDs not according to the recommended ARV dosing guidelines were ritonavir and indinavir, efavirenz, and saquinavir. Ritonavir, a PI, is used as a booster in ARV combination therapy. The concurrent administration of ritonavir that markedly inhibits CYP3A4, with another PI like saquinavir substantially increases plasma concentrations of saquinavir, thus reducing of the adverse effects, less frequent and thereby more convenient dosing, with fewer pills and food restrictions, which, in turn, may enhance patient adherence [49]. Another advantage to this is that the higher plasma PI levels may have the potential to overcome viral resistance to the PI [50].

Unfortunately there are DDIs that do occur, when two PIs are co-administered because some PIs can alter the metabolism and thus the plasma concentration of other PIs, thus creating complex drug interactions when a second PI is added to HAART [51]. In this study it was observed that ritonavir was given with other PIs in PDDs of 3000 mg, 1200 mg, 800 mg and 600 mg. The recommended dosages of 100 mg capsules or 600 mg/7.5mL solutions in adults are 600 mg every 12 hours (when ritonavir is used as sole PI). As a pharmacokinetic booster for other PIs, the dosing recommendation is 100 mg – 400 mg per day – in 1-2 divided doses [24-26, 46]. It also stated that boosted PI regimens that utilise a low dose of ritonavir (100-200 mg) appear to offer the best balance of efficacy and tolerability.

It is further argued that at the stated dose, ritonavir boosts the bioavailability of the second PI without contributing significantly to the side-effect profile of the regimen; side-effects observed with ritonavir-boosted PIs have generally been similar to those associated with boosted PI alone [51]. Therefore it is advisable to administer ritonavir in low doses, because interactions among PIs are complex. In addition to competitive inhibition, ritonavir also induces metabolising enzymes, and it is argued that for ritonavir, the extent of induction has been shown to be concentration- (or dose-) and time- dependent [52]. Adverse effects that have been reported with ritonavir were gastro-intestinal intolerance, nausea, vomiting, diarrhoea, paraesthesias – circumoral and extremities, hyperlipidemia, especially hypertriglyceridemia, hepatitis, asthenia and others [45].

Results from this study revealed that ritonavir 800 mg was administered with saquinavir 800 mg. These PDDs are not acceptable according to the treatment guidelines [25-26, 45]. Although it was reported that ritonavir when administered with saquinavir enhances the bioavailability and prolongs the elimination half-life of saquinavir such that the plasma-concentration time of saquinavir increased as much as 30- to 50-fold compared to that of saquinavir alone [52]. Therefore the recommended combination dosage of ritonavir and saquinavir was reported to be 400 mg/400 mg since this appeared to have extremely potent antiretroviral activity, judged on the basis of the documented durable responses observed in patients [54].].

In this study indinavir was administered with ritonavir at PDDs of 2400 mg and 3000 mg respectively. These doses are considered to be high considering that indinavir has a very short half-life because of the high systemic clearance; therefore the recommended dose is 800 mg every 8 hours [26]. For the same reasons mentioned above, it is administered with ritonavir to improve its bioavailability and to prolong the elimination half-life, and to reduce the total dose necessary to achieve a potent antiretroviral plasma concentration. The recommended dose for 200 mg, 333 mg and 400 mg capsules of indinavir is 800 mg every 8 hours if given alone, and with ritonavir, the dosages should be 800 mg for indinavir and 100 mg or 200 mg for ritonavir every 12 hours [24-26].

Pharmacokinetic data that were presented about variable dosage combinations of indinavir and ritonavir in which they treated antiretroviral-naïve, HIV-infected patients with a combination of indinavir 800 mg and ritonavir 100 mg twice daily and results revealed that the concentration of indinavir was 4-fold higher than with the regimen of indinavir alone, 800 mg every 8 hours [55]. The combination was well-tolerated and was significantly less expensive because fewer dosages were administered. Furthermore another author found that ritonavir had a favourable and dose-dependent effect on indinavir pharmacokinetics, at a dosage combination of 800 mg of indinavir and 200 mg of ritonavir twice daily, the trough concentration of indinavir was very high [56].

Indinavir presents the following adverse effects: nephrolithiasis, gastro-intestinal intolerance, nausea, indirect hyperbilirubinemia, headache, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia and heamolytic anaemia [26]. The dosage combinations of these two PIs have to be closely monitored considering that the two PIs interact with each other and their aggregate of the adverse effects of the boosted PI. Considering the adverse effects of both PIs this was a high number that was obtained and this could lead to treatment failure of the HIV/AIDS patient.

In this study potential DDIs were identified between ARV agents that were prescribed in different regimens according to prescriber and age groups with more GP ARV prescriptions than SP prescriptions. It was observed that a higher percentage of ARV prescriptions with potential DDIs prescribed by SPs for three years had PDDs not according to the recommended doses. It is therefore recommended that more education be provided to the prescribers in the private health care sector in South Africa for ARV agents on the recommended ARV doses as well as potential drug-drug interactions for the patients to achieve an optimal therapy.

Limitations

Some limitations of this study were the non-availability of patient clinical data to do in-depth analysis of DDIs and PDDs analysis, neither was information on HIV-naïve or –experienced patients, CD4 values and viral loads of the patients available. The data were obtained directly from the medicine claims database that does not capture these data.

Acknowledgements

Managers of PBM that provided the data for the research project.

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CHAPTER 4

CONCLUSIONS AND RECOMMENDATIONS

In this chapter the conclusions will be discussed and recommendations to interest groups will be made. These aspects will be discussed according to the specific objectives as stated in Chapter 1. Limitations of this study will also be described.

The specific objectives of the empirical study were to

- *determine the prevalence of HIV/AIDS patients in the private health care sector in SA using medicine claims databases of two PBMs;*
- *estimate the total number of ARV prescriptions and medicine items claimed through the PBM companies.;*
- *determine the prevalence of potential DDIs identified between ARVs and other drugs as well as between ARVs themselves on a prescription in this section of the private health care sector;*
- *investigate the prevalence of potential DDIs between ARV agents in different age groups;*
- *determine the influence of PMBs on the prevalence of potential DDIs between ARV agents and other drugs in a section of the private health care sector in SA;*
- *analyse the prevalence potential DDIs identified between ritonavir and other ARVs in a section of the private health care sector in SA;*
- *identify potential DDIs between ARV drugs and to determine whether PDDs can be used in the evaluatin of these interactions in a section of the private health care sector in SA;*
- *investigate the prevalence of potential DDIs between ARV drugs on prescriptions prescribed by general practitioners (GPs) and specialists (SPs) in South Africa and the evaluation of the prescribed daily doses (PDDs) of the interacting drugs; and*
- *formulate recommendations regarding management of clinically significant level 2 DDIs between ARVs in clinical practice, referring to recommended treatment guidelines.*

4.1 PREVALENCE OF HIV/AIDS PATIENTS

The first objective of the study was to determine the prevalence of HIV/AIDS patients in the private health care sector in SA using medicine claims databases of two PBMs.

The prevalence of HIV/AIDS patients from the medicine claims databases (A and B) were discussed as follows (refer to Section 1.5.10, Tables 1.3 and 1.8):

- Number of HIV/AIDS patients compared to the total number of patients that presented in the study whose prescriptions were claimed from databases A and B (refer to Table 4.1).
- The gender distribution of HIV/AIDS patients as compared to the gender distribution of patients in databases A (for 2006 only) and B (2005 to 2007) (refer to Table 4.2 and Table 4.3).
- The age distribution of HIV/AIDS patients as compared to the total age distribution of patients in database A (for 2006 only) (refer to Table 4.3)
- The age distribution of HIV/AIDS patients as compared to the total age distribution of patients in database B (for 2005 to 2007) (refer to Table 4.4).

4.1.1 Number of HIV/AIDS patients compared to the total number of patients that presented in databases A and B

The total number of HIV/AIDS patients compared to the total population in both databases is shown in Table 4.1. As shown in Table 4.1, the prevalence percentage of HIV/AIDs patients that presented in database A increased from 1.38 % for 2004 to 3.27% in 2006 and in database B increased from 0.63 % for 2005 to 1.10% for 2007. The increase of HIV/AIDS from year 2004 to 2007 is supported by the fact that the PMBs for HIV/AIDS were implemented in January 2005 in the private health care sector in SA where more people were registered for the HIV/AIDS management programmes (Da Silva & Wayburne, 2008:40).

Table 4.1: Number of HIV/AIDS patients compared to the total number of patients presented in databases A and B

Number of HIV/AIDS patients											
Database A						**Database B**					
2004 N = 657 009		2005 N = 379 352		2006 N = 275 424		2005 N = 1 218 358		2006 N = 1 259 099		2007 911 212	
n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
9065	1.38	9290	2.45	8 999	3.27	7 664	0.63	10 162	0.81	10 061	1.10

**Percentage of HIV patients was calculated according to the total number of patients in a specific per year in database A or B*

N = Total number of patients on database A or B

n = Number of HIV/AIDS patients

4.1.2 Gender distribution of patients that presented in databases A and B

The gender distribution of patients whose prescriptions were claimed from database A is shown in Table 4.2 and for database B is shown in Table 4.3 and Table 4.4. As demonstrated in Tables 4.2, 4.3 and 4.4, there was female predominance over males whose prescriptions were claimed through the medicines claims databases. According to South African Census 2001, there were more females than males in SA in 2001 (Statistics South Africa, 2008:5). This is further confirmed by a report from Statistics SA that by mid-year 2008, SA had a population of 48.7 million, of which 52% were females and 48% were males (Statistics South Africa, 2008:5). Furthermore estimates released in the National and Provincial Indicators for 2006 by Dorrington *et al.* (2006:10) indicated that the prevalence of HIV/AIDS was higher for women than for men for the 15 to 34 year age group. However, the results in Table 4.2 reveal that the there were more male (32.42%) than female (28.81%) HIV/AIDS patients in database A for 2006. This may be because of the large percentage of cases where the gender was unknown.

Table 4.2: Gender distribution of patients in database A for 2006

Gender	Number of patients		Number of HIV/AIDS patients	
	N	%*	N	%*
Female	77 889	28.28	2593	28.81
Male	69 159	25.11	2917	32.42
Unknown gender	128 375	46.61	3489	38.77
Total	**275 424**	**100.00**	**8999**	**100.00**

%*: *Percentage was calculated according to the total number of patients per gender distribution in database A for 2006.*

n = *Number of HIV/AIDS patients according to gender in database A for 2006.*

As observed in Tables 4.3 and 4.4, the gender distribution of both the total number of patients and HIV/AIDS patients in database B indicate that there were more females than males from 2005 to 2007. As already stated this is in accordance with statistics obtained from Statistics South Africa that by mid-year 2008, there were more females (48%) than males (42%) in SA (Statistics South Africa, 2008:5).

Table 4.3: Gender distribution of all patients in database B for 2005 to 2007

Gender	Number of patients					
	Year					
	2005		2006		2007	
	N	%*	N	%*	n	%*
Female	67 813	55.47	698 475	55.47	502 071	55.10
Male	540 874	44.39	559 531	44.44	408 734	44.86
Unknown gender	1 671	0.14	1 087	0.09	407	0.04
Total	**1 218 358**	**100.00**	**1 259 093**	**100.00**	**911 212**	**100.00**

%*: *Percentage was calculated according to the total number of patients per gender distribution in database B for 2005 to 2007.*

n = *Number of patients according to gender in database B for 2005 to 2007.*

Table 4.4: Gender distribution of HIV/AIDS patients in database B for 2005 to 2007

Gender	Number of HIV/AIDS patients					
	Year					
	2005		2006		2007	
	N	%*	N	%*	N	%*
Female	4395	57.34	5830	57.36	5922	58.86
Male	3270	42.66	4334	42.64	4139	41.14
Total	**7665**	**100.00**	**10164**	**100.00**	**10061**	**100.00**

%*: *Percentage was calculated according to the total number of HIV/AIDS patients per gender distribution in database B for 2005 to 2007.*

n = *Number of HIV/AIDS patients according to gender in database B for 2005 to 2007.*

4.1.3 Age distribution of all and HIV/AIDS patients that presented in database A

The age groups used in the study were discussed in Section 1.5.4.2. The number of HIV/AIDS patients distributed according to age group is shown in Table 4.5. Two categories of age groups were used for each database as illustrated in Section 1.5.4.2, Tables 1.5 and 1.6.

Table 4.5: Age distribution of all and HIV/AIDS patients in database A for 2006

Age group (in years)	Number of patients		Number of HIV/AIDS patients	
	N	%[a]	N	%[b]
0≤6	29 749	10.80	171	1.90
6≤12	23 451	8.51	230	2.56
12≤19	21 457	7.79	76	0.84
19≤40	93 273	33.87	3 033	33.70
40≤60	80 718	29.31	5 347	59.42
>60	16 431	5.97	142	1.58
Unknown age	10 345	3.76	-	-
Total	**275 424**	**100.00**	**8 999**	**100.00**

%[a]: *Percentage was calculated according to the number of patients in database A for 2006.*

%[b] *Percentage was calculated according to the number of HIV/AIDS patients in database A for 2006.*

As shown in Table 4.5, of the total number of patients (N = 275 424) in database A, 3.24% (n = 8 999) were HIV/AIDS patients. Furthermore, patients older than 19 years but less than 40 years represented 33.87% of all HIV patients and older than 40 years but less than 60 years represented 59.42% of all HIV patients in database A. This could also be explained by the fact that these two age groups represent the working and economically active class and could afford a medical scheme and used the private health care facilities. Furthermore these two age groups represent the most sexually active groups of society (Bradshaw *et al.* (2003:143) and probably engaged in unprotected sex, which put them at higher risk of HIV infection These results reflected the results reported by the South African Department of Health in collaboration with UNAIDS and WHO that published an updated estimate of 18.34% prevalence of HIV in people aged 15 to 49 years old in 2006 (Department of Health, 2007:9).

4.1.3 Age distribution of patients in database B

The total number of HIV patients as compared to the total number of patients in database B is shown in Table 4.6.

Table 4.6: Age distribution of all and HIV/AIDS patients in database B for 2005 to 2007

Age groups (in years)	Number of patients			Number of HIV/AIDS patients		
	Year			Year		
	2005	2006	2007	2005	2006	2007
0≤12	205 831 (16.89%[a])	202 322 (16.07%[a])	149 518 (16.41%[a])	409 (5.34%[b])	523 (5.15%[b])	488 (4.85%[b])
12≤19	122 029 (10.02%[a])	122 551 (9.73%[a])	101 218 (11.11%[a])	56 (0.73%[b])	90 (0.89%[b])	96 (0.95%[b])
19≤45	452 339 (37.13%[a])	468 573 (37.21%[a])	319 516 (35.06%[a])	5 558 (72.52%[b])	7 150 (70.36%[b])	7 084 (70.41%[b])
45≤59	244 566 (20.07%[a])	260 823 (20.72%[a])	188 901 (20.73%[a])	1 462 (19.08%[b])	2 175 (21.40%[b])	2 348 (23.34%[b])
>59	193 586 (15.89%[a])	204 809 (16.27%[a])	152 058 (16.69%[a])	179 (2.34%[b])	224 (2.20%[b])	45 (0.45%[b])
Unknown age	7 (0%[a])	20 (0%[a])	1 (0%[a])	-	-	-
Total	**1218358**	**1259099**	**911212**	**7664**	**10162**	**10061**

[a] *Percentage was calculated according to the total number of patients in each specific year*

[b] *Percentage was calculated according to the total number of HIV/AIDS patients in each specific year.*

As observed in Table 4.6, patients older than 19 years but less than 45 years had the highest of the total number of patients and the highest number of HIV/AIDS patients for the three years, followed by patients older than 40 years but less than 60 years. This is in accordance with the report given by the National Department of Health (2009:8) for HIV/AIDS prevalence per age group and showing the HIV prevalence estimates in the older age groups above 30 years. It showed a tendency towards an increase from 30.7% in 2006 to 40.4% in 2008. This could be a reflection of AIDS-related mortality beginning to relent in this particular age group due to the provision of ARV treatment.

4.2 TOTAL NUMBER OF ARV PRESCRIPTIONS

The second objective of the study was to estimate the total number of ARV prescriptions through the PBM companies.

The total number of ARV prescriptions claimed through databases A and B were discussed under the following headings (refer to Section 1.5.10, Tables 1.3 and 1.8):

- Number of ARV prescriptions claimed as compared to the total number of prescriptions (refer to Table 4.7).
- Number of ARV prescriptions in database A per age group (refer to Table 4.8).
- Number of ARV prescriptions according to the total number of ARV items per prescription in databases A and B (refer to Table 4.9).
- Number of ARV prescriptions according to the total number of ARV items per prescription and prescriber for each year in database B (refer to Table 4.10).
- Number of ARV prescriptions according to different age groups and different prescribers per year in database B (refer to Table 4.11).

4.2.1 Number of ARV prescriptions compared to the total number of prescriptions

The number of ARV prescriptions claimed from the databases as compared to the total number of prescriptions is shown in Table 4.7. As observed in Table 4.7 the number of ARV prescriptions claimed through the PBMs increased from 1.68% to 4.74% for 2004 to 2006 for database A, as well as for database B from 0.59% to 1.11% for 2005 to 2007.

Table 4.7: Number of ARV prescriptions compared to the total number of prescriptions claimed through the two PBMs for the different study years

Database A			**Database B**		
Number of ARV prescriptions			**Number of ARV prescriptions**		
Year			**Year**		
2004	**2005**	**2006**	**2005**	**2006**	**2007**
N = 2 595 254	N =1 621 739	N =993 804	N= 8 506 355	N = 9 029 912	N= 8 015 535
43 482	51 613	47 085	49 995	81 096	88 988
(1.68%)	(3.18%)	(4.74%)	(0.59%)	(0.90%)	(1.11%)

These results are supported by the fact that for database B, there was an increase in the number of HIV/AIDS prescriptions from 2005 to 2007 (refer to Section 4.1.1 and Table 4.1). Furthermore a press release from WHO/UNAIDS (2006) in 2006 stated that the number of HIV-positive patients receiving treatment was steadily increasing in Sub-Saharan Africa. This could also have been due to the effect of PMBs for HIV/AIDS had been implemented in 2005 in the private sector in SA having more people registering with the HIV/AIDS programmes as was also stated by Da Silva and Wayburne. (2008:41). This is supported by a report from UNICEF – South Africa about South African provincial HIV prevalence estimates for 2006 to 2007. According to the report, in the public sector there was an increase in HIV prevalence in KwaZulu-Natal and the Free State, the most infected areas in SA from 39.1% in 2005 to 37.4% in 2007 and from 30.3% to 33.5% in 2007 respectively (UNICEF, 2008).

4.2.2 Number of ARV prescriptions per age group in database A for 2006

The number of ARV prescriptions in database A per age group for 2006 is shown in Table 4.8. The age of patients was not available for 2004 and 2005 in database A. As shown in Table 4.8, ARV prescriptions for patients older than 40 years to equal 60 years, accounted for the highest prevalence percentage (55.61%) of all ARV prescriptions, followed by by ARV prescriptions for patients older than 19 years but less than 40 years, with 37.58% of ARV prescriptions. As already mentioned these results are confirmed by results in Tables 4.5 and 4.6 which showed that these two age groups presented with the highest percentage of HIV/AIDS patients resulting in having the highest number of ARV prescriptions (refer to Sections 4.1.3 and 4.14). Patients older than 12 years but less than 19 years had the lowest number (0.95%) of ARV prescriptions because this age group had the lowest percentage of HIV/AIDS patients as shown in Tables 4.5 and 4.6 (refer to Sections 4.1.3 and 4.1.4). It is recommended that intensive primary education on HIV/AIDS be done mostly in patients older than 19 years but less than 40 years and patients older than 40 years but less than 60 years pertaining to its prevention and its related social issues.

Table 4.8: Number of ARV prescriptions per age group in database A for 2006

Number of ARV prescriptions (N = 47 085)		
Age groups (in years)	**N**	**%***
0≤ 6	958	2.03
6≤12	1 332	2.83
12≤19	445	0.95
19≤40	17 694	37.58
40≤60	26 185	55.61
>60 years	470	1.00
Total	**47 085**	**100.00**

**Percentage was calculated according to the total number of ARV prescriptions in database A for 2006.*

4.2.3 Number of ARV items per prescription in databases A and B

The number of ARV items per prescription claimed through the two PBMs (databases A and B) are revealed in Table 4.9.

Table 4.9: Number of ARV items per prescription in databases A and B for the different study years

Number of ARV Items per prescription	ARV prescriptions					
	Database A			Database B		
	Year			Year		
	2004 N=43 482	2005 N=51 613	2006 N=47 085	2005 N=49 995	2006 N=81 096	2007 N=88 988
1	3 343 (7.69%*)	3 118 (6.04%*)	2 332 (4.95%*)	2 246 (4.49%*)	3 301 (4.07%*)	2 662 (2.99%*)
2	23 691 (54.48%*)	27 928 (54.11%*)	26 387 (56.04%*)	21 875 (43.75%*)	35 294 (43.52%*)	49 569 (55.70%*)
3	14 662 (33.72%*)	19 274 (37.34%*)	17 468 (37.09%*)	21 927 (43.87%*)	40 195 (49.56%*)	34 795 (39.10%*)
4	1 704 (3.92%*)	1 199 (2.32%*)	822 (1.74%*)	3 909 (7.82%*)	2 255 (2.78%*)	1 902 (2.14%*)
5	81 (0.19%*)	94 (0.18%*)	76 (0.18%*)	36 (0.07%*)	51 (0.06%*)	59 (0.07%*)
6	1 (0.00%*)	-	-	2 (0.00%*)	-	1 (0.00%*)

**Percentage was calculated according to the total number of ARV prescriptions claimed in a specific year in database A or B*

It is observed that the highest percentages of ARV prescriptions were with two ARV items followed by three ARV items per prescription for both databases. The standard treatment guidelines for ARV therapy recommend combination therapy because combinations of ARVs create multiple obstacles to HIV replication to keep the number of offspring low and reduce the possibility of a superior mutation (Bartlett & Lane, 2006:18; National Department of Health, 2004:6; National Department of Health, 2005:76; Regensberg & Makiwane, 2009:43).

Furthermore no individual ARV drug has been demonstrated to suppress HIV infection for an extended period, and a number of different combinations have been shown to be effective in reducing the number of opportunistic infections and delaying the onset of AIDS (Regensberg & Makiwane, 2009:43; Bartlett *et al.*, 2006a:2051). It is recommended that prescribers be educated on the standard treatment guidelines for ARV prescribing, emphasising dual and triple therapy. As stated by Bartlett *et al.* (2006a:2051) ARV therapy with three agents provide potent suppression of plasma HIV RNA levels below detectable limits in several treated patients resulting in immunologic improvements, and decreases in HIV-related complications. It is therefore recommended that ARVs agents be given in combination of three, e.g. 2 NRTIs and either an NNRTI or a PI to be able to reduce the viral load to undetectable levels.

4.2.4 Number of ARV prescriptions according to the number of ARV items per prescription and prescriber in database B for 2005 to 2007

The number of ARV prescriptions prescribed by General Practitioners (GPs) and Specialists (SPs) for each year in database B is shown in Table 4.10. Database B had data for three years 2005 to 2007.

Table 4.10: Number of ARV prescriptions according to the number of ARV items per prescription and prescriber in database B for 2005 to 2007.

Number of ARV items per prescription	Number of ARV prescriptions					
	2005		2006		2007	
	GPs N=45 954	SPs N=4 041	GPs N= 74 318	SPs N=6 778	GPs N= 80 908	SPs N = 8 080
1	1 673 (3.64%*)	573 (14.18%*)	2 523 (3.39%*)	778 (11.48%*)	2078 (2.56%*)	584 (7.23%*)
2	1 992 (43.35*)	1 952 (48.31%*)	32 083 (43.17%*)	3 211 (47.37%*)	44 876 (55.47%*)	4 693 (58.08%*)
3	20 635 (44.91%*)	1 292 (31.97%*)	37 715 (50.75%*)	2 480 (36.59%*)	32 356 (39.99%*)	2 439 (30.19%*)
4	3 692 (8.03%*)	217 (5.37%*)	1 952 (2.63%*)	303 (4.47%*)	1 550 (1.92%*)	352 (4.35%*)
5	30 (0.07%*)	6 (0.15%*)	45 (0.06%*)	6 (0.09%*)	47 (0.06%*)	12 (0.15%*)
6	1 (0.00%*)	1 (0.02%*)	0 (0.00%*)	0 (0.00%*)	1 (0.00%*)	0 (0.00%*)

**Percentage was calculated according to the total number of ARV prescription prescription by the different prescribers for per a specific year.*

GPs : General Practitioners; SPs: Specialists; ARV : Antiretroviral

As observed in Table 4.7, the percentage of ARV prescriptions claimed through the PBM (database B) increased from 0.59% in 2005 to 1.11% in 2007. It is also observed from the results in Table 4.10 that ARV prescriptions prescribed by GPs accounted for 91.92% (2005), 91.64% (2006) and 90.92% (2007) of all ARV prescriptions claimed as compared to the 8.08% (2005), 8.36% (2006) and 9.08% (2007) prescribed by SPs. This could be due the fact since this is data from a section of the private health care sector, the costs incurred to visit a GP are less compared to visiting a SP. Another possibility could be that there are more GPs than SPs in the private health care sector in SA. Therefore more HIV patients visited GPs than SPs, resulting in more GP prescriptions being claimed compared to SP prescriptions. The possible restrictions of the medical schemes on the referral system to a SP may also have limited access to SP services. It may also be that once a patient has visited the SP (and has stabilised) he or she may be referred back to a GP for further support services.

Another observation from the table is that in all the three years, the number of ARV prescriptions with the highest numbers of ARV items by both GPs and SPs were those prescriptions with 3 items followed by 2 items. As already explained the recommended therapy is "triple therapy" followed by "double therapy" (refer to see Section 4.2.3). Monotherapy is no longer recommended because of resistance (Bartlett *et al.*, 2006a:2051; National Department of Health, 2004:6; National Department of Health, 2005:76).

4.2.5 Number of ARV prescriptions according to prescriber for the different age groups in database B

The number of ARV prescriptions in database B prescribed by GPs and SPs for the different age groups for each year is shown in Table 4.11. Database B had data for three years 2005 to 2007 such data were not available from database A.

As observed in Table 4.11, the number of ARV prescriptions according to age group increased from 2005 to 2007, mostly in patients who were aged between 19 years but less than 45 years and patients who were aged between 45 years but less than 59 years. These results are supported by the report that the expected number of new HIV-positive patients per age group in SA in 2005, was peaking at ages 20 to 25 years with many AIDS related deaths peaking at ages 30 to 40 years (Johansson, 2007:1614).

It was also noted that in all three study years patients who were aged between 19 years and 45 years presented with the highest number of ARV prescriptions followed by patients who were older than 45 years but less than 59 years. These two age groups presented the working and economically active group of society and therefore could afford to be members of the medical schemes. This is also confirmed by a study performed in a public health care sector by Welz *et al.* (2007) in KwaZulu-Natal that reported the prevalence of HIV in adults (15-54 years) to have reached 23% in 2003/2004, with 27% of resident women (15-49 years) and 14% of resident men (15-54 years).

Table 4.11: Number of ARV prescriptions according to prescriber for the different age groups for 2005 to 2007 in database B

Age groups (in years)	2005		2006		2007	
	GPs N=45 954	SPs N=4 041	GPs N=74 318	SPs N=6 778	GPs N=80 908	SPs N=8 080
0≤12	2 662 (5.79%*)	372 (9.21%*)	3 914 (5.27%*)	652 (9.62%*)	4 003 (4.95%*)	741 (9.17%*)
12≤19	2 334 (0.51%*)	26 (0.64%*)	491 (0.66%*)	59 (0.87%*)	707 (0.87%*)	88 (1.09%*)
19≤45	32 471 (70.66%*)	2 884 (71.37%*)	51 188 (68.87%*)	4 209 (62.10%*)	54 391 (67.23%*)	4 792 (59.31%*)
45≤59	9 551 (20.78%*)	646 (15.91%*)	17 100 (23.01%*)	1 616 (23.84%*)	19 914 (24.61%*)	2 149 (26.59%*)
>59	1 037 (2.26%*)	113 (2.80%*)	1 625 (2.19%*)	242 (3.57%*)	1 893 (2.34%*)	310 (3.84%*)

**Percentage was calculated according to the total number of ARV prescriptions prescribed by the different prescribers for the specific year*

Furthermore, a report from the UNICEF (2008) in 2008 stated that in SA the estimated number of people living with HIV in 2005 was 55 000 of which 18.8% were adults who were in the age range of 15 to 49 years and the numbers increased from 2005 to 2007. This explains why this age group had the highest number of ARV prescriptions claimed from the database.

4.3 PREVALENCE OF POTENTIAL DRUG-DRUG INTERACTIONS

The third objective of this study was to determine the prevalence of potential DDIs identified between ARVs and other drugs as well as between ARVs themselves on a prescription in this section of the private health care sector.

The fourth objective of the study was to investigate the prevalence of potential DDIs between ARV agents in different age groups.

The prevalence of potential DDIs identified from prescriptions in the databases was discussed in terms of the following (refer to Section 1.5.10, Tables 1.3 and 1.8):

- Types of potential DDIs identified from prescriptions in the databases A for 2004 and 2005 (refer to Table 4.12).
- Prevalence of potential DDIs between ARVs and other drugs interacting at levels 1 to 5 for 2004 and 2005 on prescriptions in database A (refer to Table 4.13).
- Prevalence of potential DDIs identified between ARVs interacting at level 2 on prescriptions in database B according to different age groups for 2005 to 2007 (refer to Table 4.14).
- Prevalence of potential DDIs between ARVs and other drugs interacting at level 1 identified on prescription in database A for 2004 and 2005 (refer to Table 4.15).
- Prevalence of potential DDIs between ARVs and other drugs interacting at level 2 identified on prescriptions in database A for 2004 and 2005 (refer to Table 4.16).
- Prevalence of potential DDIs between ARVs interacting at level 2 on prescription in database A for 2004 and 2005 (refer to Table 4.17).
- Prevalence of potential DDIs between ARVs prescribed in different age groups on prescriptions in database A for 2006 (refer to Table 4.18).

4.3.1 Types of potential DDIs identified on prescriptions in database A for 2004 and 2005.

The types of DDI as identified by the guidelines by Tatro (2005:xiv) are defined in Section 1.5.5.2, Table 1.7 Section 4.3.2 as well as Section 3.3.5. Although the focus of the study was mostly on DDIs between ARV, other DDIs were also identified in certain cases.

Table 4.12: Number of potential DDIs identified in database A for 2004 and 2005

Potential DDIs identified		
Interacting drugs	**N**	**Percentage (%*)**
Between ARVs and other drugs	15 130	83.89
Between ARVs themselves	2 905	16.11
Total	**18 035**	**100.00**

**Percentage was calculated according to the total number of potential DDIs identified.*

As observed in Table 4.12, potential DDIs were identified between ARVs and other drugs because HIV-infected patients present with other conditions for which other drugs are prescribed. For example, there are interactions between ARVs and drugs used for dyspepsia, tuberculosis, cholesterol, peptic ulcers, depression and epilepsy, (Winston & Boffito, 2005:2).

There are potential DDIs between ARVs themselves particularly NNRTIs and PIs since both groups are extensively metabolised by the cytochrome P450 system, therefore there is a considerable potential for pharmacokinetic drug interactions when these drugs are administered concomitantly with other drugs metabolised via the same pathway (Seden *et al.*, 2009:5; Clarke *et al.,* 2008: HS-3; Winston & Boffito, 2005:1; De Maat *et al.*, 2003:223).

Although the standard treatment guidelines for ART (WHO, 2009b:41; Regensberg & Makiwane, 2009:70; National Department of Health, 2005:10, National Department of Health, 2004:2) recommend certain ARV combinations, there are DDIs encountered between these regimens, but these DDIs can be managed through dosage adjustments as explained later (refer to Section 4.8, Table 4.30).

4.3.2 Prevalence of potential DDIs identified between ARVs and other drugs interacting at clinical significance level 1 to 5 on prescriptions in database A for years 2004 and 2005

Potential DDIs were identified between ARVs and other drugs interacting at different clinical significance levels 1 to 5 as indentified according to guidelines by Tatro (2005:xiv) (refer to Section 1.5.5.2; Table 1.2). The frequencies of DDIs of clinical significance levels 1 to 5 identified from prescriptions in database A for year 2004 and 2005 are shown in Table 4.13 (refer to Section 1.5.10, Tables 1.3 and 1.8).

As shown in Table 4.13, the highest number of DDIs between ARVs and other drugs was identified in clinically significant level 5, followed by clinically significant level 4. According to Tatro (2005: xiv) clinically significant level 4 (major/moderate) indicates that the DDI could occur, but data are very limited, and clinically significant level 5 (minor/any), the DDI is doubtful; no good evidence of an altered clinical effect. Clinically significant level 1 (major) means that the effects are potentially life-threatening or capable of causing permanent damage, while clinically significant level 2 (moderate) indicates that the effects may cause deterioration in a patient's clinical status. Therefore additional treatment, hospitalisation, or extended hospital stay may be necessary.

Table 4.13: Potential clinically significant level 1 to 5 interactions identified between ARVs and other drugs on prescriptions in database A for 2004 and 2005

			2004		2005	
Clinically significant rating	**Severity**	**Documentation**	**N**	**%***	**N**	**%***
1	Major	Suspected or greater	16	0.09	15	0.06
2	Moderate	Suspected or greater	1436	7.96	505	2.01
3	Minor	Suspected or greater	1221	6.77	980	3.90
4	Major/moderate	Possible	6678	37.03	9864	39.25
5	Minor/any	Possible or unlikely	8684	48.15	13766	54.78
Total			**18035**	**100.00**	**25130**	**100.00**

**Percentage was calculated according to the total number of potential interactions identified in a specific year.*

4.3.3 Prevalence of potential DDIs identified between ARVs interacting at clinically significant level 2 on prescriptions in database B according to the different age groups for 2005 to 2007

The prevalence of potential DDIs identified between ARVs interacting at clinical significance level 2 on prescriptions in database B according to the different age groups is shown in Table 4.14.

Table 4.14: Number of potential DDIs between ARVs at clinically significant level 2 identified on prescription in database B according to different age groups for 2005 to 2007

Number of potential DDIs in different age groups						
Age groups (in years)	**2005**		**2006**		**2007**	
	n	**%***	**N**	**%***	**N**	**%***
0≤12	34	4.37	34	2.94	30	2.55
12≤19	8	1.03	-	-	5	0.42
19≤45	539	69.28	785	67.97	815	69.24
45≤59	175	22.49	273	23.64	251	21.33
>59	22	2.83	63	5.45	76	6.46
Total	**778**	**100.00**	**1 155**	**100.00**	**1177**	**100.00**

**Percentage was calculated according to the total number of potential DDIs identified on prescriptions for different age-groups of a specific year.*

As observed in Table 4.14, patients who were aged between 19 years and 45 years had the highest percentage of potential DDIs identified on ARV prescriptions, followed by patients who were aged between 45 years and 59 years. As already discussed in sections 4.2.4, 4.2.5 and 4.2.6, this age group received the highest number of ARV prescriptions with three ARV items. This is confirmed by a report in a retrospective review of ART therapy, through logistic regression analysis, that those patients with age exceeding 42 years, with more than three co-morbidities, and with treatment with three or more ARV medicine items or a PI, independently increased the risk for clinically significant drug interactions (Bartlett & Lane, 2006:18).

4.3.4 Prevalence of potential DDIs identified between ARVs and other drugs interacting at clinically significant level 1 on prescription from database A for 2004 and 2005

Potential clinically significant level 1 interactions were identified from database A between ARVs and other drugs for years 2004 and 2005 as reflected in Table 4.15. As shown in Table 4.15, most DDIs between ARVs and other drugs were identified in year 2004 specifically between the PIs (ritonavir, indinavir and saquinavir) and the proton pump inhihibitors (lanzoprazole), statins (simvastatin), cardiac glycoside (digoxin) and potent analgesic (fentanyl) (Katende-Kyenda *et al.*, 2008a:110).

Table 4.15: Prevalence of potential DDIs between ARVs and other drugs interacting at clinically significant level 1 on prescription from database A for 2004 and 2005.

	2004		2005	
ARVs and other drugs	**N**	**%***	**N**	**%***
Indinavir and lansoprazole	3	18	-	-
Indinavir and omeprazole	2	12	-	-
Indinavir and simvastatin	1	6	6	40
Ritonavir and simvastatin	4	24	-	-
Ritonavir and digoxin	5	28	9	60
Ritonavir and fentanyl	1	6	-	-
Saquinavir and fentanyl	1	6	-	-
Total	**17**	**100.00**	**15**	**100.00**

**Percentage was calculated according to the total number of potential interactions identified on prescriptions in a specific year.*

Simvastatin is primarily metabolised by CYP3A4, an isoenzyme inhibited by marketed HIV-1PIs, and therefore is contraindicated with all marketed HIV-1 PIs because of the potential for significant increases in exposure and potential toxicity (Fichtenbaum *et al.*, 2003:S109). This was further confirmed by Dube *et al.* (2003:613) and Davison and Toth (2004:73) who stated that the DDIs result in increased levels of statins, increasing the patient's risk for adverse effects like myalgias, rhabdomyolysis, elevated creatinine phosphokinase (CPK), and hepatic dysfunction. It is therefore recommended that lactone drugs like lovastatin and simvastatin not be co-administered with PIs, as they are avid substrates for CYP3A4 and as such their metabolism is significantly inhibited by CYP3A4 inhibitors, such as ritonavir (Fichtenbaum *et al.*, 2002:569).

The statins that are recommended for use with PIs are pravastatin, fluvastatin and rosuvastatin for their metabolism is not via oxidation by CYP3A4 (Winston & Boffito, 2005:3). It is also recommended that when initiating statin therapy in an HIV-patient, it is advisable to start with the lowest dose available and titrate up gradually in order to achieve the necessary lipid-lowering effect (Clarke *et al.*, 2008:HS-5). Other alternative lipid-lowering drugs such as fibrates, ezetimibe, or niacin are also recommended for they bypass the hepatic P450 system and undergoe different routes of metabolism, thus eliminating the potential for DDIs with ARVs (Dube *et al.*, 2003:614; Fessel *et al.*, 2002:1785; Bennett *et al.*, 2007:15).

As observed in Table 4.15, a potential interaction was identified between indinavir and lansoprazole, a proton pump inhibitor (PPI). It has been reported by Fulco *et al.* (2006:1974) and Tran *et al.* (2001:207) that acid-suppressive treatment with PPIs like lansoprazole and omeprazole can cause a decrease in the absorption of some PIs due to changes in the pH of the gastrointestinal tract. It is therefore recommended that PIs with known interactions not be prescribed with drugs used for dyspepsia. Furthermore in case of buffered drugs that alter gastric acidity or H_2-receptor antagonists, it is recommended that the two drugs be administered as far apart as possible (Winston & Boffito, 2005:2).

Administration of ritonavir and digoxin is not recommended because ritonavir decreases the total digoxin clearance levels at renal and non-renal levels. Furthermore it has been proved that therapeutic levels of ritonavir inhibit drug transport and metabolism of digoxin, a P-gp substrate, in humans (Ding *et al.*, 2004:73). It is therefore recommended that concomitant use of the two drugs is done by dose adjustment and monitoring digoxin therapeutic levels.

4.3.5 Prevalence of potential DDIs between ARVs and other drugs interacting at clinically significant level 2 identified on prescription from database A for 2004 and 2005

Drug-drug interactions (DDIs) were also identified between ARVs and other drugs interacting at clinically significant level 2 for years 2004 and 2005 as shown in Table 4.16. It was noted that, in 2004 there were more DDIs between ARVs and other drugs prescribed for other conditions presented by HIV/AIDS patients (refer to Table 4.16).

Table 4.16: Frequency of potential clinically significant level 2 DDIs between ARVs and the other drugs identified on prescription from database A for 2004 and 2005

Interacting ARVs and other drugs	2004		2005	
	N	%[a]	n	%a
Didanosine and ketoconazole	3	2.73	2	2.20
Didanosine and ofloxacin	1	0.91	2	2.20
Didanosine and ciprofloxacin	2	1.82	2	2.20
Didanosine and levofloxacin	-	-	3	3.30
Didanosine and itraconazole	3	2.73	-	-
Efavirenz and alprazolam	6	5.45	20	21.98
Efavirenz and methadone	4	3.64	-	-
Efavirenz and atorvastatin	-	-	7	13
Efavirenz and triazolam	4	3.64	-	-
Efavirenz and ethinyl astradiol	-	-	13	14.29
Indinavir and fluconazole	7	6.36	-	-
Indinavir and Itraconazole	7	6.36	-	-
Indinavir and ketoconazole	4	3.64	-	-
Lopinavir and fluconazole	2	1.82	-	-
Lopinavir and itraconazole	2	1.82	-	-
Lopinavir/ritonavir and alprazolam	1	0.91	-	-
Lopinavir/ritonavir and chlordiazepoxide	3	2.73	-	-
Lopinavir/ritonavir and diazepam	1	0.91	-	-
Lopinavir/ritonavir and fluconazole	15	13.64	7	7.69
Lopinavir/ritonavir and ketoconazole	-	-	4	4.40
Lopinavir/ritonavir and itraconazole	2	1.82	4	4.40
Nelfinavir and alprazolam	-	-	11	12.09
Ritonavir and alprazolam	3	2.73	-	-
Ritonavir and ethinyl estradiol	-	-	3	3.30
Ritonavir and chlordiazepoxide	3	2.73	-	-
Ritonavir and diazepam	1	0.91	-	-
Ritonavir and fluconazole	16	14.55	6	6.59
Ritonavir and itraconazole	2	1.82	1	1.10
Ritonavir and fluoxetine	2	1.82	-	-
Ritonavir and piroxicam	2	1.82	-	-
Ritonavir and pravastatin	2	1.82	6	6.59
Ritonavir and zolpidem hemitartate	3	2.73	-	-
Saquinavir and chlordiazepoxide	2	1.82	-	-
Saquinavir and diazepam	1	0.91	-	-
Saquinavir and fluconazole	2	1.82	-	-
Saquinavir Mesylate and fluconazole	2	1.82	-	-
Saquinavir Mesylate and alprazolam	2	1.82	-	-
Total	**110**	**100.00**	**91**	**100.00**

[a]*Percentage was calculated according to the total number of potential interactions identified on prescriptions in a specific year.*

The decrease in percentage of potential DDIs from 2004 to 2005 could be due to the effect of PMBs for HIV/AIDs that were implemented in the private health care sector of SA in 2005. This had an impact on the management of HIV/AIDS patients with the decrease in the number of potential DDIs (Da Silva & Wayburne, 2008:45).

Most potential DDIs that were identified in 2004 were between indinavir, ritonavir and azoles both accounting for 16.36% (n = 18); followed by lopinavir/ritonavir and azoles with 15.45% (n = 17) and efavirenz and benzodiazepines accounting for 9.09% (n = 10). Of the potential DDIs identified for year 2005, the highest number was with efavirenz and benzodiazepines accounting for 22.00% (n = 20); lopinavir/ritonavir with azoles with 16.5% (n = 15) and efavirenz with estrogens at 14.3% (n = 13) (refer to Table 4.16).

Administering PIs with benzodiazepines leads to a pharmacokinetic interaction in that there are large increases in serum concentrations of benzodiazepines undergoing oxidative metabolism due to inhibition of hepatic metabolism thus causing severe sedation and respiratory depression (Merry *et al.*, 1997:268). It is therefore recommended that co-administration of PIs with benzodiazepines be avoided (Merry *et al.*, 1997:268).

It was observed in this study that potential DDIs were identified between ritonavir (PI) and ethinyl estradiol (oral contraceptive) (refer to Table 4.16). Though there are limited data on the pharmacokinetic interactions between oral contraceptives and ARVs specifically the PIs, one author found in his study that ethinyl oestradiol area under the time concentration curve was reduced by 41% in healthy female volunteers during concomitant ritonavir (Ouellet *et al.*, 1998:111). Back (2005) reported similar results with nelfinavir and lopinavir/ritonavir. It is therefore recommended that physicians be cautious when prescribing oral contraceptives to patients receiving PIs because of the variations in effect on ethinyl oestradiol levels (Winston & Boffito, 2005:3). If prescribing a combined oral contraceptive for a patient on an enzyme-inducing drug, a preparation containing a higher dose - at least 50μg - of the oestrogen component should be prescribed. Another alternative is to use progestogen-only preparation. Furthermore, it is also recommended that women receiving PIs should use alternate forms of birth controls (Cohen *et al.*, 2002:45).

There are a number of well-recognised opportunistic infections that are associated with HIV infection that would need treatment or prophylaxis. There is a complication in treating fungal infections that require agents like the azoles. In the above table DDIs were identified between ketoconazole and ritonavir. When PIs are administered with azoles like fluconazole, the exposure of the azole is increased by the PIs and decreased by

NNRTIs (Seden *et al.*, 2009:6). Another author reported that ketoconazole and other azoles inhibit CYP450 metabolism and P-glycoprotein (an influx drug transport) function, therefore resulting in an increase in PI plasma exposure (Winston & Boffito, 2005:4). It is therefore recommended that among the azoles, the best option to use with the PIs is fluconazole because its effect is reduced. It is also recommended that protocols for treatment of co-infection be incorporated into the existing ARV programmes taking into consideration local drug availability (Seden *et al.*, 2009:7).

4.3.6. Prevalence of potential DDIs between ARVs themselves interacting at clinically significant level 2 identified on prescriptions from database A for 2004 and 2005

The prevalence of potential DDIs between ARVs themselves interacting at clinically significant level 2 identified from database A for years 2004 and 2005 is shown in Table 4.17.

The results presented in Table 4.17 reveal that potential DDIs between NNRTIs and PIs were the most prevalent followed by potential DDIs between NRTIs and PIs. All currently available PIs are metabolised by the cytochrome P450 system, and are also inhibitors of CYP3A4 ranging from the very weak inhibition for saquinavir to very potent ritonavir. Therefore they are predicted to have numerous drug interactions as stated by several authors (Seden *et al.*, 2009:5; Clarke *et al.*, 2008: HS-3; Miller *et al.*, 2007:1378; Winston & Boffito, 2005:1; Cohen *et al.*, 2002:43).

Table 4.17: Potential clinically significant level 2 interactions identified between ARVs on prescriptions from database A for 2004 and 2005

ARVs interacting	2005		2006	
	N	%*	N	%*
Indinavir (PI) and ritonavir (PI)	490	36.95	129	6.92
Efavirenz (NNRTI) and ritonavir (PI)	274	20.66	-	-
Efavirenz (NNRTI) and indinavir (PI)	198	14.93	83	4.46
Didanosine (NRTI) and indinavir (PI)	121	9.13	37	1.99
Efavirenz (NNRTI) and lopinavir/ritonavir (PI)	118	8.90	88	4.72
Nevirapine (NNRTI) and nelfinavir (PI)	-	-	12	0.64
Efavirenz (NNRTI) and saquinavir mesy (PI)	1	0.08	-	-
Nevirapine(NNRTI)and lopinavir/ritonavir (PI)	49	3.70	37	1.99
Nèlfinavir (PI) and nevirapine (NNRTI)	2	0.15	-	-
Nevirapine(NNRTI) and saquinavir mesy (PI)	5	0.38	-	-
Nevirapine (NNRTI)and lopinavir/ritonavir (PI)	45	3.39	37	1.99
Indinavir (PI) and lopinavir/ritonavir (PI)	9	0.68	-	-
Indinavir (PI) and nevirapine (NNRTI)	13	0.98	15	0.81
Efavirenz (NNRTI) and nelfinavir (PI)	-	-	12	0.64
Ritonavir (PI) and saquinavir (PI)	-	-	974	52.28
Efavirenz (NNRTI) and saquinavir (PI)	1	0.08	-	-
Didanosine (NRTI) and zidovudine (NRTI)	-	-	476	25.55
Total	**1326**	**100.00**	**1863**	**100.00**

**Percentage was calculated according to the total number of potential DDIs identified on prescriptions in a specific year.*

NRTI = Nucleoside reverse transcriptase inhibitor; NNRTI = Nonnucleoside reverse transcriptase inhibitor; PI = Protease inhibitor.

Although most DDIs involving HIV drugs are essentially unavoidable, many of them can be better managed by focusing on the dosage adjustments. It is therefore recommended that in some DDIs, for example those that involve efavirenz, dosage adjustments be done as was reported by Park-Wyllie *et al.* (2007:933) in managing efavirenz-based interactions with significant reductions in HIV viral load. Another example of dosage adjustment is when riotonavir is administered with saquinavir, a low dose of ritonavir is recommended for use (Gerber, 2000:S125). Furthermore, indinavir has numerous pharmacokinetic disadvantages including having a very short half-life because of the systemic clearance, and it is recommended to be given at a dose of 800 mg with ritonavir at 100 mg (Burger *et al.*, 1999: 136).

The identification of clinically significant DDIs by clinicians is fundamental to improving the quality of prescribing in HIV management. It is important for all prescribers to have access to a complete list of medications patients are taking. It is also necessary that computer programmes that contain databases of interacting drugs be available to the prescribers. It has been established that these represent a practical and effective method for detecting potential DDIs (Seden *et al.*, 2009:7).

4.3.7 Prevalence of potential DDIs identified between ARVs interacting at clinical significance level 2 in different age groups on prescription from database A for 2006

The total number of potent DDIs identified between ARVs interacting at clinical significance level 2 according to different age groups from database A is shown in Table 4.18.

As observed from Table 4.18, a total of 960 (0.68% of the total number of ARV prescriptions) potential DDIs were identified according to the age group of patients. Of these, patients in age group older than 40 but less than 60 years presented with the highest number of DDIs (60.21%). These results coincide with the results explained in Section 4.1.3 and Table 4.3, in which this age group presented with the highest number of HIV patients. Furthermore, the similar results in Section 4.2.2 and Table 4.6 give further explanation that the same age group had the highest number of ARV prescriptions that were claimed from the database.

It was also noted that DDIs were identified between ARVs interacting at clinically significant level 2 with the highest prevalence percentage identified between indinavir (PI) and ritonavir (PI) (20.73%; n = 199), followed by efavirenz (NNRTI) and lopinavir/ritonavir (PI) (6.77%; n = 65).

Table 4.18: Numbers of potential DDIs identified between ARVs interacting at clinically significant level 2 on prescriptions from database A for 2006

Age group (in years)	Number of DDIs		Interacting ARVs at clinical significance level 2	Number of DDIs	
	n	%		n	%
0 ≤6	18	1.88	Nelfinavir and nevirapine	5	1.49
6≤12	41	4.27	Saquinavir and efavirenz	1	0.30
			Saquinavir and lopinavir/ritonavir	1	0.30
			Efavirenz and lopinavir/ritonavir	22	6.55
			Nelfinavir and nevirapine	6	1.79
12≤19	6	0.63	Indinavir and ritonavir	2	0.60
19≤40	311	32.40	Efavirenz and lopinavir/ritonavir	19	5.65
			Efavirenz and indinavir	60	17.86
			Efavirenz and saquinavir	2	0.60
			Indinavir and ritonavir	7	2.08
			Saquinavir and ritonavir	5	1.49
40≤60	578	60.21	Efavirenz and lopinavir/ritonavir	14	4.17
			Efavirenz and nelfinavir	2	0.60
			Indinavir and ritonavir	188	55.95
>60	6	0.63	Indinavir and ritonavir	2	0.60
Total	**960**	**100.00**		**338**	**100.00**

As has already been explained in Section 4.3.7 and Table 4.17, these drugs belong to the group of PIs and NNRTIs and are metabolised by the CYP450 and all inhibitors of CYP3A4, therefore are expected to have numerous DDIs (Gerber, 2000:S124; Malaty & Kuper, 1999:147).

4.4 EFFECT OF PMBs ON THE PREVALENCE OF POTENTIAL DDIs BETWEEN ARVs IN A SECTION OF THE PRIVATE HEALTH CARE SECTOR

The fourth objective of this study was to determine the influence of PMBs on the prevalence of potential DDIs between ARV agents and other drugs in a section of the private health care sector in SA.

The effect of PMBs on the prevalence of DDIs of ARVs was discussed under the following headings (refer to Section 1.5.10, Tables 1.3 and 1.8):

- Number of potential clinically significant level 1 to 5 DDIs between ARVs and other drugs identified on prescriptions in database A for 2004 and 2005 (refer to Table 4.12).
- Number of potential DDIs between ARVs and other drugs interacting at clinically significant level 1 on prescription from database A for 2004 and 2005 (refer to Table 4.15).
- Number of potential DDIs between ARVs and other drugs interacting at clinically significant level 2 on prescription from database A for 2004 and 2005 (refer Table 4.16).
- Number of potential DDIs between ARVs themselves interacting at clinically significant level 2 on prescription from database A for 2004 and 2005 (refer Table 4.17).

4.4.1 The number of potential clinically significant level 1 to 5 DDIs between ARVs and other drugs and between themselves identified on prescriptions in database A for 2004 and 2005

The total number of DDIs identified interacting at clinical significance level 1 to 5 between ARVs and other drugs is shown in Table 4.12. As has already been discussed in Section 4.3.2 and as shown in the table there was a decrease in the number of potential DDIs with clinical levels 1 to 3 in 2005, and an increase in levels 4 and 5. This was due to the possible influence of the implementation of the PBM for HIV/AIDS on the prevalence of DDIs between ARVs and other drugs. With the implementation of PMB for HIV/AIDS, certain managed programmes were phased in to secure the appropriateness and effectiveness of drugs in the identified chronic diseases (Da Silva & Wayburne, 2008:41; Erasmus, 2007).

The number of potential DDIs between ARVs and other drugs interacting at level 1 is shown in Table 4.15. The prevalence of potential DDIs between ARVs and other drugs was discussed in Section 4.3.5. As observed there were more potential DDIs identified in year 2004 than in year 2005 for the reason given above. The total number of potential DDIs between ARVs and other drugs interacting at level 2 from database A is shown in Table 4.16. A discussion on the potential DDIs between ARVs and other drugs interacting at level 2 was done in Section 4.3.6. It was noted that the total number of potential DDIs in 2004 was more than DDIs indentified between ARVs and other drugs in 2005. There was also a reduction in the different types of DDIs in 2005 for the same argument as above (refer to Sections: 4.4.1; 4.4.2 & 4.4.3). The number of potential DDIs identified between ARVs interacting at clinical significance level 2 from database A is shown in Table 4.17. Potential DDIs between ARVs have already been discussed in Section 4.3.7. Several DDIs were identified between ritonavir and other ARVs especially NNRTIs, and the number of potential DDIs between ARVs decreased from 2004 from 2005 for the same reason given above (Council for Medical Schemes, 2007a).

4.5 POTENTIAL DDIs IDENTIFIED BETWEEN RITONAVIR AND OTHER ARV DRUGS IN A PRIVATE HEALTH CARE SECTOR IN SOUTH AFRICA

The fifth objective of this study was to analyse the prevalence potential DDIs identified between ritonavir and other ARVs in a section of the private health care sector in SA.

As discussed in Section 4.3.6, several DDIs were identified between ritonavir and other ARVs. For example potential DDIs were identified between ritonavir and indinavir (n = 490; 36.95%); ritonavir and efavirenz (n = 274; 20.66%) (Katende-Kyenda *et al.*, 2008a: 111; Katende-Kyenda *et al.*, 2008b:406); ritonavir and indinavir (n = 188; 55.95%) (Katende-Kyenda *et al.*, 2008c:397). Therefore this section discussed the potential DDIs between ritonavir and other ARVs identified from database A as follows (refer to Section 1.5.10):

- Number of potential DDIs between ritonavir and other ARVs as compared to the number of medicine items, ARV prescriptions, DDIs between ARVs in database A for 2004 to 2006 (refer to Table 4.19).
- The total number of potential DDIs between ritonavir (unboosted) with other ARVs on prescriptions in database A for 2004 to 2006 (refer to Table 4.20).
- The total number of DDIs between ritonavir (boosted) and other ARVs on prescription in database A for 2004 to 2006 (refer to Table 4.22).

4.5.1 Number of potential DDIs between ritonavir and other ARVs as compared to the number of medicine items, ARV prescriptions, DDIs between ARVS in database A for 2004 to 2006

The total number of potential DDIs between ritonavir and other ARVs as compared to the number of medicine items, ARV prescriptions, DDIs between ARVs on prescriptions in database A is shown in Table 4.19.

As observed in Table 4.19, the percentage of medicine items decreased from 2004 to 2006. There was an increase in the percentages for the ARV prescriptions from 2004 to 2005, then a decrease in 2006. The same trend occurred for the DDIs between ARVs and DDIs between ritonavir – unboosted and boosted. It is also noticed that 2005 presented with the highest percentage of ARV prescriptions claimed from the database, giving the highest number of DDIs between ARVs themselves and also the highest number of DDIs between ritonavir (boosted and unboosted) and other ARVs. Year 2006 had lower percentages of ARV prescriptions claimed as compared to year 2005 because there were fewer medical aids contracted as compared to year 2005, and this explains the drop in DDIs identified between ARVs themselves and ritonavir and other ARVs.

Table 4.19: Three year comparison of the total number of medicine items, ARV prescriptions, potential DDIs between ARVs and DDIs between ritonavir and other ARVs from database A for 2004 to 2006

Year	Medicine items	ARV prescriptions	DDIs between ARVs	DDIs between ritonavir – unboosted and boosted and other ARVS
2004	2 595 254 (49.81%[a])	43 482 (30.58%[b]) (1.68%)	1 326 (31.96%[c]) (3.05%)	985 (39.18%[d]) (74.28%)
2005	1 621 739 (31.12%[a])	51 613 (36.30%[b]) (3.18%)	1 863 (44.90%[c]) (3.61%)	1 265 (50.32%[d]) (67.90%)
2006	993 804 (19.07%[a])	47 085 (33.12%[b]) (4.74%)	960 (23.14%[c]) (2.04%)	264 (10.50%[d]) (27.50%)
Total	**5 210 797**	**142 180**	**4 149**	**2 514**

%[a]: Percentage was calculated according to the total number of medicine items claimed from 2004 to 2006

%[b]: Percentage was calculated according to the total number of ARV prescriptions claimed from 2004 to 2006

%[c] :Percentage was calculated according to the total number of ARV DDIs identified from 2004 to 2006

%[d]: Percentage according to the number of DDIs between ritonavir and other ARVs identified from 2004 to 2006

4.5.2 Number of potential DDIs between ritonavir (unboosted) with other ARVs on prescriptions in database A for 2004 to 2006

The number of potential DDIs between ritonavir (unboosted) with other ARVs claimed from database A is shown in Table 4.20. Ritonavir (unboosted) signifies when given alone and boosted when combined with another drug.

Table 4.20: Prevalence of prescriptions with potential DDIs between ritonavir-unboosted and other ARVs for 2004 to 2006

Interacting ARVs	2004		2005		2006	
	n	%*	N	%*	N	%*
Ritonavir and saquinavir	-	-	974	85.44	5	2.45
Ritonavir and indinavir	490	60.57	129	11.34	155	97.55
Ritonavir and efavirenz	274	33.87	-	-	-	-
Ritonavir and nevirapine	45	5.56	37	3.25	-	-
Total	**809**	**100.00**	**1140**	**100.00**	**204**	**100.00**

**Percentage was calculated according to the total number of potential interactions identified in a specific year*

As observed in Table 4.20, year 2005 had the highest percentages of prescriptions with potential DDIs between ritonavir-unboosted and other ARVs, as it was the year with the highest percentages of ARV prescriptions claimed from the database, followed by 2004 and 2006 respectively. Potential DDIs between ritonavir and other drugs interacting at clinically significant level 1 were discussed in Section 4.3.5 and Table 4.15. Thereafter followed another discussion on the prevalence of prescriptions with potential DDIs between ritonavir and other drugs interacting at clinically significant level 2 in Section 4.3.6 and Table 4.16. Then in Section 4.3.7 and Table 4.17 ritonavir was discussed to have had the highest number of prevalence of prescriptions with potential DDIs with other ARVs interacting at clinically significant level 2.

As shown in Table 4.20, the highest percentages of prescriptions with potential DDIs were identified between ritonavir-unboosted and saquinavir, followed by ritonavir, indinavir, efavirenz and nevirapine. Potential DDIs between ritonavir-unboosted and saquinavir presented at clinically significant level 3 (minor), with mild effects, without significantly affecting the therapeutic outcome. Saquinavir as the first PI to be marketed in USA has very unfavourable pharmacokinetics, because its efficacy has been very limited because of the low and variable plasma concentrations achieved. However, its pharmacokinetics was reported to have improved when combined with ritonavir (Hsu *et al.*, 1998:375). Thus ritonavir enhances the bioavailability and prolongs the elimination half-life of saquinavir such that the plasma-concentration time/area under the curve (AUC) of saquinavir increased as much as 30- to 50-fold as compared to saquinavir alone (Merry *et al*, 1997:F29). Ritonavir, in comparison with other PIs, produces the largest increase in saquinavir plasma concentrations (Lichterfeld *et al.*, 2002:37), thus may increase adverse effects of saquinavir. It is noted that the highest percentage of potential DDIs was identified between ritinavir and indinavir in 2004. Though DDIs have been identified between the two PIs, the administration of ritonavir improves the biovailability and prolongs the elimination half-life of indinavir at 400 mg twice daily (Gerber, 2000:S125). Furthermore the

prevalence of prescriptions with potential DDIs were identified between ritonavir and efavirenz and nevirapine both NNRTIs. This combination is recommended because both groups as stated by Moyle and Back (2001:105) have potent ARV efficacy and are not antagonistic.

4.5.3 Number of potential DDIs between ritonavir (boosted) with other ARVs on prescriptions in database A for 2004 to 2006

The number of potential DDIs between ritonavir (boosted) with other ARVs on prescriptions from database A is shown in Table 4.21. The other regimens where most potential DDIs were identified were between ritonavir- boosted, co-formulated as lopinavir/ritonavir and efavirenz (n = 118, 88, 34) for 2004 to 2006; nevirapine (n = 49, 37) for 2004 and 2005; indinavir (n = 9) for only 2004 and saquinavir (n = 22) for only 2006.

Table 4.21 Potential DDIs between ritonavir-boosted and other ARVs on prescriptions in database A for 2004 to 2006

Interacting ARVs	2004		2005		2006	
	n	%*	n	%*	N	%*
LPV/RTV and efavirenz	118	67.05	88	70.40	34	98.21
LPV/RTV and nevirapine	49	27.84	37	29.60	-	-
LPV/RTV and indinavir	9	5.11	-	-	-	-
LPV/RTV and saquinavir	-	-	-	-	22	1.79
Total	**176**	**100.00**	**125**	**100.00**	**56**	**100.00**

**Percentage was calculated according to the total number of prescriptions with potential DDIs identified in a specific year.*

LPV/RTV: lopinavir/ritonavir

Lopinavir has a negligible bioavailability and a short half-life when used alone, but it achieves therapeutic concentrations when combined with low-dose ritonavir (Oldfield & Plosker, 2006:1276). In addition to the benefits of twice-daily dosing and a reduced dosage burden because of co-formulation of lopinavir and ritonavir, lopinavir together with ritonavir has been proved to be safe and effective (Hsu *et al.*, 2003:350).

Results from this study showed that lopinavir/ritonavir was prescribed together with efavirenz, in the three-year period presenting potential DDIs (Table 4.21). Both efavirenz and lopinavir/ritonavir are inhibitors and inducers of CYP-mediated metabolism. Thus a potential DDI with efavirenz may result in an increased or decreased concentration of PIs. Management of this DDI would involve increasing the lopinavir/ritonavir

dose by 33% during co-administration with efavirenz compensating for the enzyme inductive effect of efavirenz, resulting in reduced lopinavir levels with the standard lopinavir/ritonavir dose of 400/100 mg twice daily (Hsu *et al.*, 2003:351).

The second highest number of prescriptions with potential DDIs was between ritonavir and indinavir (see Table 4.21). Indinavir is a potent HIV PI; however, it is also extensively and rapidly metabolised by CYP3A (Solas *et al.*, 2002:374). It is given as an 800 mg dose every 8 hours; however, the regimen still results in low and variable minimum concentration values. It is therefore administered with ritonavir, to improve the bioavailability and to prolong the elimination half-life of indinavir, and in this way would reduce the total dose necessary to achieve a potent ARVplasma concentration (Acosta, 2002:S11).

In conclusion, the PIs are extensively metabolised by the CYP 450 enzymes, therefore drug-interactions involving PIs will occur largely as a result of enzyme induction or enzyme inhibition. The results of this study showed that ritonavir, a potent inhibitor of CYP3A4, presents potential DDIs when prescribed with other ARVs in this section of the private health care sector, and therefore it is recommended that these potential DDIs be markedly managed by dose adjustments.

4.6 POTENTIAL DDIs BETWEEN ARV DRUGS AND USING PDDs IN THE EVALUATION OF THESE INTERACTIONS IN THE PRIVATE HEALTH CARE SECTOR IN SA.

The sixth objective of this study was to identify potential DDIs between ARVs and to determine whether PDDs can be used in the evaluation of these interactions in a section of a private health care sector in SA.

Potential DDIs identified between ARVs and PDDs used in the management of these DDIs using database B were discussed as follows (refer to Section 1.5.10, Tables 1.3 and 1.8):

- Number of potential DDIs identified according to the number of ARV items per prescription for years 2005 to 2007 (database B) (refer to Table 4.13).
- Number of potential DDIs identified between ARVs according to different age groups for years 2005 to 2007 (database B) (refer to Table 4.14).
- Prescribed daily doses of potential interacting ARVs at clinical significance level 2 according to patient age group for year 2005 (database B) (refer to Table 4.22).
- Prescribed daily doses of potential interacting ARVs at clinical significance level 2 according to patient age group for year 2006 (database B) (refer to Table 4.23).

- Prescribed daily doses of potential interacating ARVs at clinical significance level 2 according to patient age group for year 2007 (database B) (refer to Table 4.24).

4.6.1 Number of potential DDIs identified per number of ARV items per prescription for years 2005 to 2007 (database B)

The number of potential DDIs identified according to the number of ARV items per prescription from database B as shown in Table 4.13 has already been discussed in Section 4.3.3.

4.6.2 Number of potential DDIs identified between ARVs according to different age group for years 2005 to 2007 (database B)

The total number of potential DDIs identified between ARVs according to different age groups claimed from database B for years 2005 to 2007 as shown in Table 4.14 has already been discussed in Section 4.3.4.

4.6.3 Prescribed daily doses of potential ARV DDIs interacting at clinically significant level 2 according to patient age group for year 2005 (database B)

The total number of ARV prescriptions with the most potential DDIs identified between ARV combinations and their PDDs are shown in Tables 4.22 to 4.24. All the prescriptions with potential DDIs identified between ARVs were interacting at clinical significance level 2 according to guidelines by Tatro (2005: X1). As observed in the three tables for the three years, potential DDIs were mostly identified between combinations of lopinavir/ritonavir (LPV/RTV) and efavirenz (EFV) followed by indinavir (IND) and ritonavir (RTV), then RTV and EFV. As already stated LPV/RTV (PI) and EFV (NNRTI) combinations are therapeutically among the highest risk-factors for DDIs, due to potent inhibition or induction of liver enzymes, such as the cytochrome P450 izoenzyme (CYP450) that metabolises many other drugs. Therefore DDIs involving PIs and NNRTIs are more likely attributable to hepatic metabolic pathways (Seden *et al.*, 2009:5; Clarke *et al.*, 2008: HS-3; Gerber *et al.*, 2005:307; Fletcher *et al.*, 2000:2495).

It should also be noted that HIV-1 PIs are widely used in combination therapy for the management of HIV-1 infection and due to their metabolism being through the CYP450 isoenzyme and their gastric absorption being pH dependent, they are prone to clinically significant drug interactions with each other (Winston & Boffito, 2005:1). It is therefore recommended to understand potential DDIs that may occur with the use of combinations of PIs and NNRTIs. It was also observed that in all three years, most prescriptions with potential DDIs were identified between LPV/RTV at PDD 799.8 mg/198 mg and EFV 600 mg, followed by

IND 1600 mg and RTV 200 mg, and RTV 200 mg and EFV 600 mg. Furthermore all these combinations were mostly identified in patients in age group (19≤45 years) followed by patients in age group (45≤59 years). In this regard the dose for lopinvir/ritonavir with efavirenz is regarded as high and could lead to toxic levels. It is therefore recommended that the dose be adjusted to LPV/RTV 400 mg/200 mg (2 tablets or 5 ml) twice a day or LPV/RTV 800 mg/200 mg (4 tablets or 10 ml) once daily for ARV-naïve patients, not patients receiving EFV, NVP, fAPV or NFV (Bartlett & Lane, 2006).

It was evident that EFV was prescribed with IND or LPV/RTV. According to the guidelines developed by the Department of Health and Human Services (DHHS), regimens containing EFV together with IND or LPV/r are not recommended because of pharmacokinetic interactions, drug toxicities, and drug resistance issues. It is recommended that if this regimen is prescribed, then dosage adjustment has to be done (Ian & Coffey, 2009).

Other drug regimens where DDIs were identified were between IND at PDD of 1600 mg and RTV at PDD of 200 mg prescribed to patients in age group 19≤45 years. The dose for IND was relatively high and could lead to the patient's developing nephrolithiasis (Gerber, 2000:S123).

Table 4.22: Prescribed Daily Doses (PDD) of potential interacting ARV combinations (clinically significant level 2) according to different patient age groups for 2005

Age group (years)	Number of prescriptions	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0≤12	8	Lopinavir/Ritonavir[i]	800 mg/200 mg	Efavirenz[ii]	200 mg
	11		400 mg/100 mg		250 mg
	5		480 mg/120 mg		250 mg
	6		480 mg/120 mg		300 mg
	4	Lopinavir/Ritonavir[i]	320 mg/80 mg	Nevirapine[iii]	2600 mg
12≤19	8	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
19≤45	144	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	36		1066.4 mg/264 mg		600 mg
	2		1142.6/mg/282.9mg		600 mg
	1		533.2 mg/132 mg		300 mg
	1		3999 mg/990 mg		1200 mg
	1		4500 mg / 3999 mg		1800 mg
	2	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Nevirapine[iii]	400 mg
	17		1066.4 mg/264 mg		400 mg
	2		799.8 mg/198 mg		500 mg
	1		1066.4 mg/264 mg		500 mg
	66	Ritonavir[v]	200 mg	Efavirenz[ii]	600 mg
	14		280 mg		600 mg
	3		300 mg		600 mg
	1		300 mg		1800 mg
	1		200 mg		80 mg
	1		240 mg		600 mg
	2		600 mg		600 mg
	113	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
	8		1600 mg		280 mg
	7		1600 mg		800 mg
	3		800 mg		200 mg
	7		800 mg		280 mg
	2		1600 mg		300 mg
	1		800mg		1200 mg
	1		2400 mg		200 mg
	1		1600 mg		240 mg
	1		2400 mg		3000 mg
	2		800 mg		800 mg
	78	Indinavir[iv]	1600 mg	Efavirenz[ii]	600 mg
	4		2400 mg		600 mg
	1		2400 mg		1800 mg
	4		280 mg		600 mg
	9		800 mg		600 mg
	1		1600 mg		1200 mg
	1		1600 mg		80 mg
45≤59	59	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	16		1066.4 mg/264 mg		600 mg
	1		799.8 mg/198 mg		307 mg
	1	Lopinavir/Ritonavir[i]	1066.4 mg/264 mg	Nevirapine[iii]	500 mg
	24	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
	7		800 mg		200 mg
	2		1600 mg		280 mg
	1		2400 mg		300 mg
	25	Indinavir[iv]	1600 mg	Efavirenz[ii]	600 mg
	6		800 mg		600 mg
	31	Ritonavir[v]	200 mg	Efavirenz[ii]	600 mg
	2		280 mg		600 mg
>59	5	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	2	Indinavir[iv]	2400 mg	Efavirenz[ii]	600 mg
	3	Lopinavir/Ritonavir[i]	1066.4 mg/264 mg	Nevirapine[iii]	400 mg
	12	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg

Table 4.22: Prescribed Daily Doses (PDD) of potential interacting ARV combinations (clinically significant level 2) according to different patient age groups for 2005 (continued)

i Kaletra® 400 mg/100 mg/5ml; Kaletra® 80 mg/20 mg cap
ii Stocrin® 50 mg cap, 200 mg cap and 600 mg tab
iii Aspen Nevirapine®; Aspen Nevirapine® 200 mg; Cipla Nevirapine® 200 mg tab,oral susp; Viramune® 200 mg tab; Viramune oral®
iv Crixivan® 200 mg cap,400 mg cap
v Norvir® cap; Norvir® syr

Table 4.23: PDD of potential interacting ARV combinations (clinically significant level 2) according to different patient age groups for 2006

Age group (years)	Number of prescriptions	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0≤12	6	Lopinavir/Ritonavir[i]	800 mg/200 mg	Efavirenz[ii]	200 mg
	2		400 mg/100 mg		250 mg
	1		480 mg/120 mg		200 mg
	1		480 mg/120 mg		100 mg
	2		480 mg/120 mg		250 mg
	13		480 mg/120 mg		300 mg
	3	Lopinavir/Ritonavir[i]	320 mg/80 mg	Nevirapine[iii]	2600 mg
	4		799.8 mg/198 mg		400 mg
	2	Didanosine[vi]	40 mg	Indinavir[iv]	1000 mg
19≤45	283	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	126		1066.4 mg/264 mg		600 mg
	3		533.2 mg/132 mg		600 mg
	2	Lopinavir/Ritonavir[i]	799.8 mg/198 mg		1600 mg
	9		799.8 mg/198 mg	Nevirapine[iii]	400 mg
	1		1244 mg/308 mg		400mg
	42		1066.4 mg/264 mg		400mg
	1		799.8mg / 198 mg		307mg
	107	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
	14		1600 mg		800 mg
	6		800 mg		200 mg
	3		800 mg		280 mg
	14		1600 mg		280 mg
	4		1600 mg		100 mg
	3	Indinavir[iv]	2400 mg	Efavirenz[ii]	600 mg
	8		800 mg		600 mg
	63		1600 mg		600 mg
	59	Ritonavir[v]	200 mg	Efavirenz[ii]	600 mg
	14		280 mg		600 mg
	3		600 mg		600 mg
	11	Didanosine[vi]	400 mg	Indinavir[iv]	1600 mg
	4		250 mg		1600 mg
	5		100 mg		1600 mg
45≤59	86	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	33		1066.4 mg/264 mg		600 mg
	7		1066.4 mg/264 mg		400mg
	1		266.6 mg/66 mg		600 mg
	4		799.8 mg/198 mg		400 mg
	24	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
	21		800 mg		200 mg
	5		2400 mg		300 mg
	1		2400 mg		280 mg
	23	Indinavir[iv]	1600 mg	Efavirenz[ii]	600 mg
	18		800 mg		600 mg
	31	Ritonavir[v]	200mg	Efavirenz[ii]	600 mg
	10	Didanosine[vi]	400 mg	Indinavir[iv]	1600 mg
	4		250 mg		1600 mg
	5		100 mg		1600 mg
>59	25	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	9		1066.4 mg/264 mg		400 mg
	1		399.9 mg/99 mg		600 mg
	2		1066.4 mg/264 mg		500mg
	17	Indinavir[iv]	1600mg	Ritonavir[v]	200mg
	9	Ritonavir[v]	200 mg	Efavirenz[ii]	600 mg

Table 4.23: PDD of potential interacting ARV combinations (clinically significant level 2) according to different patient age groups for 2006 (continued)

i Kaletra® 400 mg/100 mg/5ml; Kaletra® 80 mg/20 mg cap
ii Stocrin® 50 mg cap, 200 mg cap and 600 mg tab
iii Aspen Nevirapine®; Aspen Nevirapine® 200 mg; Cipla Nevirapine® 200 mg tab,oral susp; Viramune® 200 mg tab; Viramune oral®
iv Crixivan® 200 mg cap,400 mg cap
v Norvir® cap; Norvir® syr
vi Aspen®didanosine 25mg 50mg, 100mg, 150mg, Videx® 100mg chew, 150mg chew, 50mg chew, 50mg chew, 250mg EC cap, 400mg EC cap, 2mg Paed susp

Table 4.24: PDD of potential interacting ARV combinations (clinically significant level 2) according to different patient age groups for 2007

Patient age group (years)	Number of prescriptions	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0< = 12	1	Lopinavir/Ritonavir[i]	480mg/120 mg	Efavirenz[ii]	300 mg
	9		640mg/160 mg		350 mg
	1		480mg/120 mg		200 mg
	6		799.8mg/198 mg		200 mg
12<=19	5	Lopinavir/Ritonavir[i]	799.8mg/198 mg	Nevirapine[iii]	400 mg
19<=45	228	Lopinavir/Ritonavir[i]	799.8mg/198 mg	Efavirenz[ii]	600mg
	145		1066.4mg/264mg		600 mg
	3		1599.6.4mg/396 mg		600 mg
	24	Lopinavir/Ritonavir[i]	799.8mg/198 mg	Nevirapine[iii]	400 mg
	8		1066.4mg/264mg		400 mg
	9		799.8mg/198 mg		500mg
	53	Ritonavir[v]	200 mg	Efavirenz[ii]	600mg
	9		280 mg		600 mg
	2		300 mg		600 mg
	3		600 mg		600 mg
	4		800 mg		600 mg
	3	Indinavir[iv]	800 mg	Ritonavir[v]	300 mg
	13		800 mg		200 mg
	3		1600 mg		100 mg
	60		1600 mg		200 mg
	9		1600 mg		280 mg
	2		1600 mg		800mg
	3	Indinavir[iv]	800 mg	Efavirenz[ii]	600 mg
	36		1600 mg		600 mg
	18	Saquinavir[vii]	800 mg	Retinovir	800 mg
	6		1200 mg		100 mg
	23		2000 mg		200 mg
45<=59	91	Lopinavir/Ritonavir[i]	799.8mg/198 mg	Efavirenz[ii]	600 mg
	17		1066.4mg/264 mg		600 mg
	3	Lopinavir/Ritonavir[i]	799.8mg/198 mg	Nevirapine[iii]	400 mg
	20	Indinavir[iv]	800 mg	Ritonavir[v]	200 mg
	15		1600 mg		200 mg
	9		2400 mg		280 mg
	11	Indinavir[iv]	800 mg	Efavirenz[ii]	600 mg
	16		1600 mg		600 mg
	26	Ritonavir[v]	200 mg	Efavirenz[ii]	600mg
	13	Saquinavir[vii]	800 mg	Retinovir	800 mg
	4	Saquinavir[vii]	800 mg	Efavirenz[ii]	600 mg
>59	26	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Efavirenz[ii]	600 mg
	4	Lopinavir/Ritonavir[i]	799.8 mg/198 mg	Nevirapine[iii]	400mg
	8		1066.4mg/264 mg		500 mg
	6	Indinavir[iv]	1600 mg	Ritonavir[v]	200 mg
	13	Ritonavir[v]	200 mg	Efavirenz[ii]	600 mg
	13	Saquinavir[vii]	2000 mg	Efavirenz[ii]	600 mg

i Kaletra® 400 mg/100 mg/5ml; Kaletra® 80 mg/20 mg cap
ii Stocrin® 50 mg cap, 200 mg cap and 600 mg tab
iii Aspen Nevirapine®; Aspen Nevirapine® 200 mg; Cipla Nevirapine® 200 mg tab,oral susp; Viramune® 200 mg tab; Viramune oral®
iv Crixivan® 200 mg cap,400 mg cap
v Norvir® cap; Norvir® syr
vi Aspen®didanosine 25mg 50mg, 100mg, 150mg, Videx® 100mg chew, 150mg chew, 50mg chew, 50mg chew, 250mg EC cap, 400mg EC cap, 2mg Paed susp
vii Invi-Rase® 200mg Cap

4.7 Prevalence of potential DDIs between ARV drugs on prescriptions prescribed by general practitioners (GPs) and specialists (SPs) in South Africa and the evaluation of the prescribed daily doses (PDDs) of the interacting drug on database B for 2005 to 2007.

The seventh objective of this study was to investigate the prevalence of potential DDIs between ARV drugs on prescriptions prescribed by general practitioners (GPs) and specialists (SPs) in SA and the evaluation of the prescribed daily doses (PDDs) of the interacting drugs. .

The prevalence of potential DDIs between ARVs on prescriptions prescribed by GPs and SPs and evaluation of PDDs of the interacting drugs were discussed as follows (refer to Section 1.5.10, Tables 1.3 and 1.8):

- Number of ARV prescriptions according to the number of ARV items per prescription and prescriber for 2005 to 2007 for database B (refer to Table 4.9).
- Number of ARV prescriptions according to prescriber and different age groups for database B for 2005 to 2007 (refer to Table 4.10).
- Number of ARV prescriptions with potential DDIs (clinically significant level 2) according to age group and prescriber for database B for 2005 to 2007 (refer to Table 4.25).
- Number of ARV prescriptions with DDIs prescribed by GPs and SPs with PDDs not according to recommended ARV dosing and age group for database B for 2005 (refer to Table 4.26).
- Number of ARV prescriptions with DDIs prescribed by GPs and SPs with PDDs not according to the recommended ARV dosing and age group for database B for 2006 (refer to Table 4.27).
- Number of ARV prescriptions with DDIs prescribed by GPs and SPs with PDDs not according to the recommended ARV dosing and age group for database B for 2007 (refer to Table 4.28).

4.7.1 Number of ARV prescriptions according to the number of ARV items per prescription and prescriber for 2005 to 2007 for database B

Number of ARV prescriptions according to the number of ARV items per prescription and prescriber for 2005 to 2007 for database B had already been discussed in Section 4.2.5 and shown in Table 4.9.

4.7.2 Number of ARV prescriptions according to prescriber and different age groups for database B

The number of ARV prescriptions prescribed according to prescriber and different age group claimed from the PBM (database B) for 2005 to 2007 as shown in Table 4.10 was discussed in Section 4.2.6.

4.7.3 Number of ARV prescriptions with potential DDIs (clinical significance level 2) according to age group and prescriber

The number of ARV prescriptions with potential DDIs (clinically significant level 2) according to age groups and prescriber for database B for 2005 to 2007 is shown in Table 4.25.

Table 4.25: Number of ARV prescriptions with potential DDIs (clinical significant level 2) according to age group and prescriber for database B for 2005 to 2007

Age group (in years)	2005		2006		2007	
	GPs N = 681	SPs N = 97	GPs N= 976	SPs N = 179	GPs N = 981	SPs N = 196
0≤12	23 (3.38%*)	11 (11.34%*)	27 (2.77%*)	7 (3.91%*)	17 (1.73%*)	13 (6.63%*)
12≤19	8 (1.17%*)	0 (0.00%*)	0 (0.00%*)	0 (0.00%*)	5 (0.51%*)	0 (0.00%*)
19≤45	467 (68.58%*)	72 (74.23%*)	648 (66.39%*)	137 (76.53%*)	664 (67.68%*)	151 77.04%*)
45≤59	165 (24.23%*)	10 (10.31%*)	249 (25.51%*)	24 (13.41%*)	225 (22.94%*)	26 (13.27%*)
>59	18 (2.64%*)	4 (4.12%*)	52 (5.33%*)	11 (6.15%*)	70 (7.14%*)	6 (3.06%*)

**Percentage was calculated according to the total number of ARV prescriptions with potential DDIs according to prescriber for the specific year.*

As shown Table 4.25, of the number of potential DDIs (N= 778) identified between ARVs prescribed in 2005, 87.53% were prescribed by GPs and 12.47% by SPs. For year 2006, the total number of potential DDIs identified between ARVs was 1 155, of which, 84.50% were prescribed by GPs and 15.50% by SPs. In 2007, of the total number of potential DDIs (N = 1 117) identified between ARVs, 83.35% were prescribed by GPs and 16.65% prescribed by SPs.

As observed in the three years, the majority of potential DDIs were identified in GP prescriptions to patients in the age group 19≤45 years followed by patients in the age group 45≤59 years (refer to Table 4.25).

As shown in Table 4.25, the percentage of ARV prescriptions with potential DDIs (clinically significant level 2) stayed approximately the same during the three years studied, i.e. between 1.6% (2005) and 1.3% (2007) of ARV prescriptions. Most of the ARV prescriptions with potential DDIs were prescribed for the three years by GPs as compared to potential DDIs identified in ARV prescriptions prescribed by SPs. This could be explained by the fact that most of the ARV prescriptions prescribed during the three years were prescribed by GPs. However, the percentage of ARV prescriptions with potential DDIs prescribed by GPs decreased from 87.53% to 83.35% and those prescribed by SPs increased from 12.47% to 16.65% for the study years 2005 to 2007. It is therefore recommended that more education and information pertaining to ARV prescribing and its complications such as DDIs be supplied to prescribers.

According to Palella *et al.* (1998:853), DDIs are of particular concern in patients infected with HIV who are receiving HAART. Although the combination of ARVs is a potent and effective therapy for HIV infection, unfortunately, ARV drugs frequently interact among themselves because many of them are metabolised through the CYP450 systems, with CYP3A4, CYP2D, and CYP2C9/19, the primary isoenzymes involved in the drugs' metabolism (Badri *et al.*, 2006:1254; Chandwani & Shutter, 2008:1023). These interactions determine positive or negative consequences resulting in recommendations to avoid some combinations or to adjust the dosage of co-administered drugs.

4.7.4 Number of ARV prescriptions with potential DDIs prescribed by GPs and SPs with PDDs not according to the recommended ARV dosing and age group for 2005 (database B)

The number of ARV prescriptions with potential DDIs prescribed by GPs and SPs with PDDs not according to the recommended ARV dosing and age group for 2005 is shown in Table 4.26. The highest percentage of ARV prescriptions with potential DDIs and PDDs not according to the recommended ARV dosing guidelines were identified in regimens with potential DDIs between lopinavir/ritonavir at PDDs 1066.4 mg/264 mg and efavirenz at PDD 600 mg for both GPs (30.30%) and SPs (6.06%) prescriptions prescribed to patients in age group (19≤45 years).

Table 4.26: Number of ARV prescriptions with potential DDIs prescribed by GPs and SPs with PDDs not according to recommended ARV dosing for different age groups for 2005

GENERAL PRACTITIONERS					
Age group (years)	**Number of prescriptions (N =681)**	**ARV combinations**			
		ARV medicine item	**PDD**	**ARV medicine item**	**PDD**
0≤12	8	Lopinavir/Ritonavir	800 mg/200 mg	Efavirenz	200 mg
	4	Lopinavir/Ritonavir	320 mg/80 mg	Nevirapine	2600 mg
19≤45	30	Lopinavir/Ritonavir	1066.4 mg/264 mg	Efavirenz	600 mg
	1		4500 mg/3999 mg		1800 mg
	15	Lopinavir/Ritonavir	1066.4 mg/264 mg	Nevirapine	400 mg
	1		1066.4 mg/264 mg		500 mg
	1	Ritonavir	300 mg	Efavirenz	1800 mg
	1	Indinavir	2400 mg	Ritonavir	3000 mg
	2		800 mg		800 mg
	1	Indinavir	2400 mg	Efavirenz	1800 mg
45≤59	16	Lopinavir/Ritonavir	1066.4 mg/264 mg	Efavirenz	600 mg
	1	Lopinavir/Ritonavir	1066.4 mg/264 mg	Nevirapine	500 mg
>59	3	Lopinavir/Ritonavir	1066.4 mg/264 mg	Nevirapine	400 mg
Total	84				
SPECIALISTS					
Age group (years)	**Number of prescriptions (N = 97)**	**ARV combinations**			
		ARV medicine item	**PDD**	**ARV medicine item**	**PDD**
19≤45	6	Lopinavir/Ritonavir	1066.4 mg/264 mg	Efavirenz	600 mg
	2		1142.6 mg/282 mg		600 mg
	1		3999 mg/990 mg		1200 mg
	2	Lopinavir/Ritonavir	1066.4 mg/264 mg	Nevirapine	400 mg
	2		799.8 mg/198 mg		500 mg
	1	Indinavir	800 mg	Ritonavir	1200 mg
	1	Indinavir	1600 mg	Efavirenz	1200 mg
Total	15				

4.7.5 Number of ARV prescriptions with potential DDIs prescribed by GPs and SPs with PDDs not according to the recommended ARV dosing and age group for 2006 (database B)

The number of ARV prescriptions with DDIs prescribed by GPs and SPs with PDDs not according to the recommended ARV dosing and age group for 2006 is shown in Table 4.27.

Table 4.27: Number of ARV prescriptions with potential DDIs prescribed by GPs and SPs with PDDs not according to recommended ARV dosing for different age groups for 2006

GENERAL PRACTITIONERS					
Age group (years)	**Number of prescriptions (N = 976)**	**ARV combinations**			
		ARV medicine item	**PDD**	**ARV medicine item**	**PDD**
0≤12	**6**	Lopinavir/Ritonavir	**800 mg/200 mg**	Efavirenz	**200 mg**
	3	Lopinavir/Ritonavir	**320 mg/80 mg**	Nevirapine	**2600 mg**
19≤45	**101**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	26	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
	1		**1244 mg/308 mg**		**400 mg**
	2		**799.8 mg/198 mg**		**1600 mg**
	14	Indinavir	**1600 mg**	Ritonavir	**800 mg**
	3	Ritonavir	**600 mg**	Efavirenz	**600 mg**
45≤59	**11**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	7	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**400 mg**
>59	**9**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**400 mg**
	2	Lopinavir/Ritonavir	**1066.4 mg/264 mg**		**500 mg**
Total	183				
SPECIALISTS					
Age group (years)	**Number of prescriptions (N = 179)**	**ARV combinations**			
		ARV medicine item	**PDD**	**ARV medicine item**	**PDD**
19≤45	**25**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
	16	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Nevirapine	**400 mg**
45≤59	**22**	Lopinavir/Ritonavir	**1066.4 mg/264 mg**	Efavirenz	**600 mg**
Total	63				

As indicated in Table 4.27, the highest percentage of ARV prescriptions with potential DDIs and PDDs not according to the recommended ARV dosing were identified in ARV regimens with potential DDIs between lopinavir/ritonavir at PDD 1066.4 mg/264 mg and efavirenz at PDD 600 mg in 41.06% of GPs prescriptions and 10.16% SPs prescriptions prescribed to patients in age group 19≤45 years.

4.7.6 Number of ARV prescriptions with potential DDIs prescribed by GPs and SPs with PDDs not according to the recommended ARV dosing and age group for 2007 (database B)

The number of ARV prescriptions with potential DDIs prescribed by GPs and SPs with PDDs not according to the recommended ARV dosing and age group for 2007 is shown in Table 4.28. As indicated in the table, the highest percentage of ARV prescriptions with potential DDIs and PDDs not according to the recommended ARV dosing guidelines were identified in ARV regimens with DDIs between lopinavir/ritonavir at PDD 1066.4 mg/264 mg and efavirenz at PDD 600 mg in GPs (47.85%) and SPs (7.59%) prescriptions prescribed to patients in age group 19≤45 years.

Table 4.28 Number of ARV prescriptions with potential DDIs prescribed by GPs and SPs with PDDs not according to recommended ARV dosing for different age groups for 2007

GENERAL PRACTITIONERS					
Age group (years)	Number of prescriptions (N = 981)	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
0≤12	9	Lopinavir/Ritonavir	640 mg/160 mg	Efavirenz	350 mg
	6	Lopinavir/Ritonavir	799.8 mg/198 mg		200 mg
19≤45	145	Lopinavir/Ritonavir	1066.4 mg/264 mg	Efavirenz	600 mg
	3	Lopinavir/Ritonavir	1599.6 mg/264 mg	Efavirenz	600 mg
	8	Lopinavir/Ritonavir	1066.4 mg/264 mg	Nevirapine	400 mg
	9	Lopinavir/Ritonavir	799.8 mg/198 mg		500 mg
	2	Indinavir	1600 mg	Ritonavir	800 mg
	18	Saquinavir	800 mg	Efavirenz	800 mg
45≤59	17	Lopinavir/Ritonavir	1066.4 mg/264 mg	Efavirenz	600 mg
	13	Saquinavir	800 mg	Ritonavir	800 mg
>59	8	Lopinavir/Ritonavir	1066.4 mg/264 mg	Nevirapine	500 mg
Total	238				
SPECIALISTS					
Age group (years)	Number of prescriptions (N = 196)	ARV combinations			
		ARV medicine item	PDD	ARV medicine item	PDD
19≤45	23	Lopinavir/Ritonavir	1066.4 mg/264 mg	Efavirenz	600 mg
	16	Lopinavir/Ritonavir	1066.4 mg/264 mg	Nevirapine	400 mg
45≤59	22	Lopinavir/Ritonavir	1066.4 mg/264 mg	Efavirenz	600 mg
	3	Lopinavir/Ritonavir	1066.4 mg/264 mg	Nevirapine	400 mg
>59	1	Lopinavir/Ritonavir	3999.9 mg/990 mg	Efavirenz	600 mg
Total	65				

After identification of DDIs between ARVs in different regimens, further investigation was done to determine those ARV regimens with DDIs containing PDDs that were not according to the recommended ARV dosing and results obtained are shown in Tables 4.26 to 4.28. Although the percentage of ARV prescriptions with potential DDIs (level 2) stayed approximately the same, the prevalence of those ARV prescriptions with DDIs where the prescriptions had ARV combinations with PDDs not according to the recommended ARV dosing (DHHS, 2006:15; DHHS:122, 2008) for the different age groups increased from 12.72% in 2005 to 25.74%. Further analysis indicated that the prevalence of ARV prescriptions with potential DDIs and PDDs not according to the recommended ARV dosing prescribed by GPs increased dramatically from 12.33% in 2005 to 24.26% in 2007 of ARV prescriptions with DDIs prescribed by GPs. Those prescribed by SPs increased from 15.46% in 2005 to 35.30% in 2006 and decreased to 33.16% in 2007.

As was observed in Tables 4.26 to 4.28 for the three years, the highest number of PDDs not according to the recommended ARV dosing with potential DDI were identified in ARV combinations of lopinavir/ritonavir at

PDD 1066.4 mg / 264 mg with efavirenz at PDD 600 mg; nevirapine at PDD 400 mg. Thereafter, for indinavir 1600 mg with ritonavir 800 mg; ritonavir 600 mg with efavirenz 600 mg; saquinavir 800 mg with efavirenz 800 mg for both GPs and SPs with the highest number of prescriptions prescribed by GPs to patients in age group 19≤45 years, followed by patients in age group 45≤59 years. Furthermore, the highest number of ARV prescriptions with potential DDIs and PDDs prescribed not according to recommended ARV dosing had been prescribed to patients in age group 19≤45 years accounting for 67.68% (n = 67) for 2005; 76.42% (n = 246) for 2006 and 73.93% (n = 224) for 2007.

As observed in Tables 4.26 to 4.28, the most commonly prescribed ARV drug with DDIs was co-formulated lopinavir/ritonavir. This was the first and only coformulated HIV-1 PI. It was reported in a review that large clinical trials have demonstrated lopinavir/ritonavir's clinical efficacy in both antiretroviral-naïve and –experienced patients (Chandwani & Shuter, 2008:1023). The immunologic and virologic benefits of treatment with this agent have been proved in HIV-infected adults, adolescents and children (Oldfield & Plosker, 2006:1293). It is strongly recommended that resistance testing of this drug be done in ART-experienced patients prior to initiation of therapy.

As observed in Tables 4.26 to 4.28, GPs prescribed lopinavir/ritonavir for patients in age group (0≤12 years). One of the limitations of this study was that the weights of the patients (particularly for children) were not available; therefore it was not clear at what weight and specific age of patients this coformulation was prescribed. Otherwise the safety, efficacy, and pharmacokinetic profiles of lopinavir/ritonavir in paediatric patients below the age of 6 months have not been established (De Maat *et al.*, 2003:223). It was assumed that patients were older than 6 months on receiving LPV/RTV 800 mg/200 mg and efavirenz (EFV) 200 mg; LPV/RTV 320 mg/80 mg and nevirapine 2600 mg and LPV/RTV 640 mg/160 mg; 799.8 mg/198 mg with EFV 350 mg; 200 mg, respectively. According to the treatment guidelines for the management of HIV-infected children, formulated by the National Department of Health South Africa in 2005, the recommended paediatric dose for LPV/RTV is <15 kg = 12 mg lopinavir/kg and ≥15 kg = 10 mg lopinavir/kg twice daily. In this case LPV/RTV was prescribed at a higher PDD considering one capsule of LPV/RTV to be 133.3 mg/33.3 mg, and the maximum dose should be 3 capsules (399.9 mg/99.9 mg) (National Department of Health, 2005:82). It is therefore recommended that ARV dosing for LPV/RTV be adhered to in order to avoid problems of toxicity.

Results from this study demonstrated that GPs prescribed lopinavir/ritonavir at PDDs 1066.4 mg/264 mg; 4500 mg/3999 mg; 1599.6 mg/264 mg to patients in age group (19≤45 years) for the three years studied. The standard adult dose of lopinavir/ritonavir is 400 mg/100 mg (2 tablets or 5 ml) twice daily or lopinavir/ritonavir 800/200 mg (4 tablets or 10ml) once daily (Department of Health, 2004:15). In this study

it was therefore given at higher PDDs. Another limitation of this study was that information about HIV-naïve or –experienced patients was not available from the database. Otherwise once-daily dosing for lopinavir/ritonavir is only recommended for treatment-naïve patients, not for patients receiving efavirenz, nevirapine or nelfinavir. When lopinavir/ritonavir is given with efavirenz or nevirapine, the recommended dose for treatment-experienced patients is 600 mg/150 mg (3 oral tablets twice daily or 533 mg/133 mg) (6.7ml oral solution) twice daily with food (National Department of Health, 2004:15; Regensberg & Makiwane, 2009:45; Chandwani & Shuter, 2008:1023).

Unfortunately there are DDIs that do occur, when two PIs are co-administered because some PIs can alter the metabolism and thus the plasma concentration of other PIs, thus creating complex drug interactions when a second PI is added to HAART (Hsu *et al.*, 1997:898). In this study it was observed that ritonavir was given with other PIs in PDDs of 3000 mg, 1200 mg, 800 mg and 600 mg. The recommended dosages of 100 mg capsules or 600 mg/7.5 ml solutions in adults are 600 mg every 12 hours (when ritonavir is used as sole PI). As a pharmacokinetic booster for other PIs, the dosing recommendation is 100 mg to 400 mg per day , in 1 to 2 divided doses (National Department of Health, 2004:14; Fisch *et al.*, 2007:325). It also stated that boosted PI regimens that utilise a low dose of ritonavir (100-200 mg) appear to offer the best balance of efficacy and tolerability. Once again it is recommended that ARV dosing for ritonavir be adhered to.

Results from this study revealed that ritonavir 800 mg was administered with saquinavir 800 mg. These PDDs are not acceptable according to the treatment guidelines (DHHS, 2006:15). Although it was reported that ritonavir when administered with saquinavir enhances the bioavailability and prolongs the elimination half-life of saquinavir such that the plasma-concentration time of saquinavir increased as much as 30- to 50-fold compared with that of saquinavir alone (Merry *et al.*, 1997:F29).

Therefore the recommended combination dosage of ritonavir and saquinavir was reported to be 400 mg/400 mg since this appeared to have extremely potent antiretroviral activity, judged on the basis of the documented durable responses observed in patients (Burger *et al.*, 1999:336). Based on this report ritonavir 800 mg is a higher dose since ritonavir is poorly tolerated at high doses, also considering the DDI that occurs between the two combinations as was reported in a study that analysed the potential DDIs between ritonavir and other ARVs and reported 85.44% (n = 974) of the total number of DDIs identified in the study (Katende-Kyenda *et al.*, 2009a:1). It is therefore recommended that ritonavir used as a booster should be prescribed at a low dose of 100 to 200 mg since at this dose it appears to offer the best balance of efficacy and tolerability (Young, 2005:290).

In this study indinavir was administered with ritonavir at PDDs of 2400 mg and 3000 mg, respectively. These doses are considered to be high considering that indinavir has a very short half-life because of the high systemic clearance; therefore the recommended dose is 800 mg every 8 hours (Hsu *et al.*, 1998:453). For the same reasons mentioned above, it is administered with ritonavir to improve its bioavailability and to prolong the elimination half-life, and to reduce the total dose necessary to achieve a potent antiretroviral plasma concentration. The recommended dose for 200 mg, 333 mg and 400 mg capsules of indinavir is 800 mg every 8 hours if given alone, and with ritonavir, the dosages should be 800 mg for indinavir and 100 mg or 200 mg for ritonavir every 12 hours (McNicholl & Coffey, 2009).

As it was observed that most DDIs were identified in ARV combinations containing lopinavir/ritonavir, it is therefore recommended that further research be done on lopinavir/ritonavir prescribing in HIV/AIDS. Prescription-medication errors resulting in overdosing of ARV agents could lead to serious adverse effects, thus not achieving the main treatment goals for ARV therapy in HIV/AIDS patients (Purdy *et al.*, 2000:833). It is therefore recommended that more education be provided to the prescribers in the private health care sector in SA for ARV agents on the recommended ARV doses for the patients to achieve an optimal therapy.

4.8 FORMULATE RECOMMENDATIONS REGARDING MANAGEMENT OF LEVEL 2 CLINICALLY SIGNIFICANT DDIS BETWEEN ARVS IN CLINICAL PRACTICE, REFERRING TO RECOMMENDED TREATMENT GUIDELINES

The eighth objective of this study was to formulate recommendations regarding management of clinically significant level 2 DDIs between ARVs in clinical practice, referring to recommended treatment guidelines.

4.8.1 Recommendation to manage potential DDIs in the private health care sector

The following recommendations have been formulated to manage these DDIs, based on the standard treatment guidelines for ARVs (refer to Section 1.5.10, Tables 1.3 and 1.8):

- Patients must be informed about the importance of consulting their doctors before using over-the-counter drugs that might interact with their prescribed ARVs.
- The prescriber should always review all patients' drugs that are prone to interact with ARVs and check for potential DDIs before prescribing any concomitant drug to a patient who is on ARV therapy.
- Drug level monitoring of concurrent patients' medications should be done.
- The identification of clinically significant DDIs by clinicians is fundamental to improving the quality of prescribing in HIV management. It is important for all prescribers to have access to a complete list

of medications patients are taking. It is also necessary that computer programmes that contain databases of interacting drugs be available to the prescribers. It has been established that these represent a practical and effective method for detecting potential DDIs (Seden *et al.*, 2009:7).

- It is recommended that physicians be cautious when prescribing oral contraceptives to patients receiving PIs because of the variations in effect on ethinyl oestradiol levels (Winston & Boffito, 2005:3). If prescribing a combined oral contraceptive to a patient on an enzyme-inducing drug, a preparation containing a higher dose (at least 50μg) of the oestrogen component should be prescribed.
- It is also recommended that among the azoles, the best option to use with the PIs is fluconazole because its effect is reduced. It is also recommended that protocols for treatment of co-infection be incorporated into the existing ARV programmes, taking into consideration local drug availability (Seden *et al.*, 2009:7).
- DDIs must be considered a major concern to the health care providers especially those caring for HIV/AIDS patient. It is therefore recommended that multiple reminders and warnings be available whenever more than two medicines are administered.
- Furthermore pharmacists and physicians need to be vigilant for DDIs, to both that are already documented and to those that are predictable from pharmacokinetic profiles, especially in patients receiving PIs.
- From all the above discussions it is recommended that to effectively treat HIV/AIDS patients, and obtain a desired health outcome, clinicians need to understand the mechanisms of DDIs pertaining to ARV agents. Prescribers need to be reminded that certain ARV agents require dosage adjustments (or pharmacokinetic enhancement) when co-administered with other drugs. Finally some drug combinations are contraindicated.
- While DDIs involving HIV drugs are essentially unavoidable, many can be managed through dosage adjustments as recommended by McNicholl and Coffey, 2009; Young 2005:288; Cohen, 2002:47; Seden *et al.*, 2009:7; Moyle & Back, 2001:106; Gerber, 2000:S125, Winston & Boffito, 2005:2; Clarke *et al.*,2008:HS-4; Chandwani & Shuter, 2008:1026; Oldfield & Plosker, 2006:1282, as illustrated in Table 4.29:

Table 4.29: Recommended dosage adjustments of interacting ARV drugs identified in the study

Drug	Co-administered drug	Dosage adjustment
Efavirenz	Lopinavir/ritonavir	No dose adjustment is necessary, when lopinavir/ritonavir at 400 mg/100 mg and 533 mg/133 mg with efavirenz are administered (Young, 2005:289). Administer efavirenz 600mg QD with lopinavir/ritonavir 400 mg /100 mg BID for ARV-naïve patients or 600 mg/150 mg for ARV-experienced patients (National Department of Health, 2004:15; Regensberg & Makiwane, 2009:45; Chandwani & Shuter, 2008:1023). Administration of lopinavir/ritonavir 800 mg/200 mg once a day with efavirenz or nevirapine not recommended (Oldfield & Plosker, 2006:1281).
Nevirapine	Lopinavir/ritonavir	Administer lopinavir/ritonavir at 533 mg/133 mg and nevirapine 200 mg (Ministry of Health, 2003:47).
Indinavir	Ritonavir	Administer ritonavir 400 mg + indinavir 400 mg twice daily (Hsu *et al.*, 1998:454).
	Lopinavir/ritonavir	Increase the dosage for indinavir to 1000 mg Q8H and lopinavir/ritonavir to 533 mg/133 mg BID (Faragon & Piliero, 2003: 433).
Ritonavir	Nevirapine	Additional doses of ritonavir 200 mg or 400 mg twice daily can be used with nevirapine (Young, 2005:288).
	Efavirenz	Add ritonavir as a booster at 100 mg QD (Faragon & Piliero, 2003:434)

Table 4.29: Recommended dosage adjustments of interacting ARV drugs identified in the study (continued)

Saquinavir	Lopinavir/ritonavir	The combination of saquinavir and lopinavir/ritonavir is safe from drug interactions, therefore no dosage adjustment required (Boffito *et al*, 2005b:1).
	Ritonavir	Saquinavir 1000 mg combined with low dose ritonavir 100 mg can be administered once or twice a day (Ministry of Health, 2003:17; Gerber, 2000:S125; Moyle & Back, 2001:108).
	Efavirenz	Dosage adjustment of saquinavir not established; administer efavirenz 600 mg QD with saquinavir 1000 mg BID (McNicholl & Coffey, 2009).
	Nevirapine	Dosage adjustment of saquinavir not established, however administer saquinavir 400 mg BID + ritonavir 400 mg BID; nevirapine 200 mg BID (Cooper *et al*., 2003:1195).

BID: twice a day; TID: three times a day; QD: once a day

4.8.2 Recommendations for further research

The following recommendations have been formulated for futher research

- Since several potential DDIs have been identified between ARVs and other drugs and between ARVs themselves in the private sector, further studies to be performed in the public health care sector of SA to make comparisons with the results obtained in the private sector.
- Conduct a study on the prescribing of lopinavir/ritonavir as a PI co-formulation commonly prescribed and presenting with several DDIs with other drugs.
- Further studies to be done on patient clinical data carrying out in-depth analysis of DDIs and PDDs.
- Further research to engage on pharmacokinetic studies of DDIs to investigate the occurrence of adverse drug interactions. as a results of DDI.
- Further research to investigate the prevalence of potential drug-disease interactions with ARV drugs in the private health care sector.
- Further studies to engage on possible reasons why the recommended ARV dosing is not adhered to in the private health care sector in SA.

- Investigate factors that could contribute to ARV prescribing medication errors among prescribers.
- Further studies to determine the cost implication of DDI between ARVs themselves and ARVs and other drugs in the private health care sector of SA.
- Further studies to formulate policies that would enforce prescribers in the private health care sector of SA to adhere to recommended ARV therapy guidelines.

4.9 LIMITATIONS AND SHORTCOMINGS OF THE STUDY

The following limitations and shortcomings should be taken into account when evaluating the results and conclusions of this study:

- All the data obtained from the pharmacy benefit management companies databases were considered to be accurate and correct.
- External validity is limited, implying that the results can only be generalised to the specific databases and study population in the private health care sector of SA.
- Demographic data were limited to patient age and gender. Certain patients (especially in database A) were not classified in age groups as their age was not recorded in the data, and those "unknown" patient data were excluded from calculations. Certain patients' gender (especially in database A) was not recorded in the data, and those "unknown" patient data were excluded from calculations.
- Two different age bands were used in the study which could have influenced the results of the study.
- It was not possible to determine PDDs of ARVs on database A because of the non-availability of drug dosages and amounts prescribed.
- It was not possible to do in-depth analysis of DDI and PDDs because of the non-availability of patient clinical data such as patients' weight, information regarding HIV-naïve or –experienced patients, CD4 values and viral loads of the patients. The data were obtained directly from thes databases of the PBM that does not capture these data.
- The clinical relevance of the identified DDIs was evaluated according to criteria stated in the literature. No clinical evaluation of the real effects of these interactions was possible. However, the results emphasized the possibility of potential DDIs that could have led to severe problems.

4.10 CHAPTER SUMMARY

This chapter focused on the discussion of the integrated results as presented in the research articles in Chapter 3. The general findings of the study were discussed according to the empirical objectives as outlined in the study. For each research objective, results were briefly discussed; conclusions and limitations of the

study highlighted and recommendations made (refer to Sections 4.1 to 4.7). Finally general recommendations have been made on the management of ARV-ARV interactions in clinical practice (refer to Section 4.8). Lastly suggestions have been made on possible issues for further research. Thereby the objectives of this study were met.

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ABSTRACTS ACCEPTED FOR PODIUM AND POSTER PRESENTATIONS AT CONFERENCES

ABSTRACT 1:

Katende-Kyenda NL, Lubbe MS, Serfontein JHP, Truter I. **The Role of Pharmacists as educators in the Management of Drug-Drug Interactions of Antiretroviral Agents** (Poster presentation).

7th International Conference on Life Long Learning in Pharmacy, University of Hertfordshire, England, 1-4 July 2007

The Role of Pharmacists as educators in the Management of Drug-Drug Interactions of Antiretroviral Agents.

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Background

Drug-drug interactions (DDIs), the main causes of adverse effects, account for 3%-7% of hospital admissions, increasing morbidity and mortality, and are common concerns of both HIV/AIDS patients and their health care providers.[1] Pharmacists as members of the health care team, play a vital role as educators in educating health care providers about the basic drug pharmacokinetic interactions, side effects and toxicities, alerting them to potential signs and symptoms that may cause serious health problems.

The aim of this study is to develop an educational tool based on the data identified from the pharmaceutical care approaches used for patients on antiretroviral (ARV) medicines.[2] The tool will be used to improve the pharmacist's management of DDIs of ARVs.

Methodology

A non-experimental, quantitative, retrospective study was performed on data obtained from a medicine claiming database for the year 2004 for all patients prescribed with ARVs, focusing on the prevalence of DDIs between ARVs and co-administered drugs and also ARVs themselves. DDIs were classified according Tatro (2005) in his book, "Drug Interactions – Facts and Comparisons."

An educational tool (Subjective, Objective Assessment and Plan (SOAP)) will be developed based on this approach to considering DDIs in the management of HIV/AIDS patients and making patient-specific decisions. This tool will educate pharmacists about "A Collaborative Management Model" which is central to the pharmacist's role in his/her communication and coordination with other members of the health care team. By using this tool, pharmacists may directly influence clinical management of DDIs by providing information obtained during patient encounters, and provide important pharmacological information to support decision making by clinicians and improve patient care.

Results

A total of 5 305 882 medicine items were prescribed, of these 1.92%, (N=101 938) were ARVs. Of the 2 595 254 prescriptions, 1.68%, (N=43 482), were ARVs. A total of 18 035 DDIs were identified, of these

interactions, 83.89%, (n=15 130), were DDIs between ARVs and co-administered drugs, while 16.11% (n=2 905) were DDIs between ARVs themselves. Possible DDIs with a clinical significance level of 1 (n=17) and 2 (n=1 436) represented 8.06% (n=1 453) of the total number of DDIs. Level 1 interactions were between: i) indinavir (PI) and lanzoprazole, omeprazole, simvastatin; ii) ritonavir (PI) and simvastatin, digoxin, fentanyl; iii) saquinavir (PI) and fentanyl. The most prevalent clinical significance level 2 DDIs found between ARVs themselves were: i) indinavir (PI) and ritonavir (PI); efavirenz (NNRTI) and ritonavir (PI); efavirenz (NNRTI) and indinavir (PI); didanosine (NRTI) and indinavir (PI); and efavirenz (NNRTI) and lopinavir/rotonavir (PI).

Discussion

The results of the study demonstrated the increase on ARV drug regimen and concomitant co-administered drug use in HIV/AIDS, resulting in DDIs. Pharmacists as members of the healthcare team who play a vital role in the clinical management of DDIs in ARVs may use SOAP, as an educational tool, to develop pharmacy action plans like gathering and reviewing patient's previous and current medication list, checking for any potential DDIs, identifying and classifying them, and providing important pharmacological information to clinicians, and developing a plan for DDIs management.

Also this tool may be as used by pharmacists to counsel patients, monitoring them for any increased adverse effects and educating them about potential DDIs, thus increasing adherence to HIV/AIDS treatment regimes and improving patient care.

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ABSTRACT 2:

Katende-Kyenda NL, Lubbe MS, Serfontein JHP & Truter I. **A two-year comparative study on the prevalence of drug-drug interactions of antiretroviral agents by using a medicine claims database** (Oral presentation).

Academy of Pharmaceutical Sciences 28th Annual Congress, Club Mykonos, Cape Town. 4-7 September 2007.

A two-year comparative study on the prevalence of drug-drug interactions of antiretroviral agents by using a medicine claims database

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Purpose:

The main aim of the study was to determine and compare the prevalence of possible drug-drug interactions (DDIs) between antiretroviral (ARV) agents themselves and other drugs on prescriptions claimed, and the possible impact of Prescribed Minimum Benefits (PMBs) and Chronic Disease List (CDL) implementation in a section of the private health care sector in South Africa.

Method:

A comparative, quantitative, retrospective drug utilization study was performed on 43 482 and 51 613 ARV prescriptions claimed through a medicine claims database during the years 2004 and 2005. respectively. The possible DDIs found in this study were classified according to the clinical significant rating as described by Tatro (2005).

Results:

A total number of 5 305 882 medicine items were claimed during 2004 and 3 606 992 medicine items claimed during 2005. For 2004, 1.92% (N = 101 938 of the medicine items were ARV drugs and for 2005, 3.38% (N = 122 062). Of a total of 2 595 254 prescriptions (for the year 2004), 1.68% (N = 43 482), were ARVs. For the year 2005, the total number of prescriptions were 1 621 736 of which 3.18% (N = 51 613) were ARV prescriptions.

For the year 2004, a total number of 18 035 DDIs were identified, of these, 83.89%, (n = 15 130) were DDIs between ARVs and other medications, while 16.11% (n = 2 905) were DDIs between ARVs themselves. Possible DDIs with clinical significance level of 1 (major, n = 17) and 2 (moderate, n = 1 453) represented 8.06% (n = 1 448) of the total number of DDIs. For the year 2005, a total number of 25 130 DDIs were identified, of these, 92.59%, (n = 23 267) were DDIs between ARVs and other drugs, while 7.14% (n = 1

863) were DDIs between ARVs themselves. Possible DDIs with clinical significance level 1 (n = 15) and 2 (n = 504) represented 2.07% (n = 519) of the total number of DDIs identified for the year 2005.

Conclusion:

The results revealed that there was a decrease in DDIs between ARVs themselves for the year 2005 (a year after the implementation of PMBs for HIV) (7.14%) as compared to 2004 (a year before PMBs implementation for HIV) (16.11%), indicating the impact of disease management programmes that were introduced in order to provide a comphrensive management approach for HIV/AIDS patients contracted with medical schemes.

ABSTRACT 3:

Katende-Kyenda NL, Lubbe MS, Serfontein JHP & Truter I. **Prevalence of Drug-Drug interactions (DDIs) between Antiretroviral Agents in different age groups in a setting of the Private Health Care Sector in South Africa for the year 2006** (Oral presentation).

PharmaTox 2007 Congress (South African Pharmacology and Toxicology Congress 2007), Buffelspoort, North-West Province, 2-5 October 2007.

Prevalence of Drug-Drug interactions (DDIs) between Antiretroviral Agents in different age groups in a setting of the Private Health Care Sector in South Africa for the year 2006

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Purpose:

Highly active antiretroviral therapy (HAART) has dramatically improved the prognosis of Human immunidefiency virus infections (HIV), though the combination of these drugs can present with potential drug-drug interactions (DDIs). The aim of this study was to determine the prevalence of DDIs between antiretroviral (ARV) drugs in different age-groups in a section of a private primary healthcare sector in South Africa.

Methods:

A quantitative, retrospective drug utilisation review was performed on 47 085 ARV prescriptions claimed through a medicine claims database during 2006. The DDIs found were classified according to a clinical significance rating as described by Tatro (2005).

Results:

An average of 5.23 ± 3.86 ARV prescription (n = 47 085) were claimed during 2006 for 8 999 HIV patients (3.27% of the total number of patients, N = 275 424). ARV prescriptions represented 4.73% of the total number of prescriptions claimed during the study period (N = 993 804). HIV patients received an average of 2.36 ± 0.61 ARVs per prescription. Only 4.95% of the prescriptions had only one ARV medicine item, 56% had two, 37% had three, 1.75% had four and < 1% had more than four ARV medicine items.

A total number of 960 DDIs were identified, of these, 1.88% were for age group 1, 4.27% for age group 2, 0.63% for age group 3, 32.40% for age group 4, 60.21% for age group 5 and 0.63% for age group 6, with age group 5 having the highest number of DDIs and age group 6 the lowest. The majority of DDIs between the ARVs presented in significance levels 2 and 4 (Moderate and Major/moderate). The most important interactions were between: indinavir and ritonavir (n = 196); efavirenz and lopinavir/ritonavir (n = 80) and efavirenz and indinavir (n = 64) all interacting at clinical significance level 2.

Conclusion:

The results of this study emphasize the importance of using drug utilisation study as an identification tool to provide insight into the prescribing and utilization patterns of antiretroviral drugs, in order to provide optimal therapy for patients infected with HIV.

ABSTRACT 4:

Katende-Kyenda NL, Lubbe MS, Serfontein JHP, Truter I. **The prevalence of possible drug-drug interactions between ritonavir and other ARVs in a private healthcare sector in South Africa** (Poster presentation). 22nd Annual Conference of the South African Association of Hospital and Institutional Pharmacists, (SAHIP), Champagne Sports Resort, Drakensburg, 6-9 March 2008.

Prevalence of possible drug-drug interactions between ritonavir and other antiretroviral drugs in a private health care sector in South Africa

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Background: The introduction of human immunodeficiency virus (HIV) protease inhibitors (PIs) has led to a dramatic decline in the morbidity and mortality associated with HIV infection, though concomitant use of PIs and other antiretrovirals (ARVs) can be complicated by drug-drug interactions (DDIs), adversely affecting levels of PIs.

Objective: To determine the prevalence of possible DDIs between ritonavir and other ARVs in a section of the private healthcare sector in South Africa, for a period of three years.

Study design: A quantitative, retrospective drug utilisation study was performed using data obtained from a medicine claims database during 2004, 2005 and 2006. The data consisted of 2 595 254, 1 621 739 and 993 804 prescriptions claimed during 2004, 2005 and 2006 respectively. The possible DDIs found were identified using the classification by Tatro (2005).

Results: The percentage prevalence of ARV prescriptions claimed increased from 1.92% (n = 43 482) during 2004, to 3.38% (n = 51 613) during 2005 and to 4.73% (n = 47 085) during 2006. A total of 1 326, 1 863 and 960 were possible DDIs identified between ARVs themselves for 2004, 2005 and 2006 respectively. Ritonavir presented with the most possible DDIs accounting for 70.89% (n = 940) for 2004, 13.63% (n = 254) for 2005; and 27.50% (n = 264) for 2006. The highest prevalence of DDIs identified was between ritonavir and indinavir (n = 490, 129, 199) for 2004 to 2006); efavirenz (n = 274, 60) for 2004 and 2006; ritonavir/lopinavir (co-formulated) and efavirenz (n = 118, 88, 65) for 2004 to 2006, nevirapine (n = 49, 37) for 2004 and 2005 and indinavir (n = 9) for only 2004. All were interacting at clinical significance level of 2.

Conclusions: These findings indicate that concomitant use of protease inhibitors like ritonavir, a potent cytochrome P450 (CYP) 3A4 enzyme inhibitor, and other ARVs is complicated by possible DDIs and therefore further studies need to be done on the management of these DDIs.

ABSTRACT 5:

Katende-Kyenda NL, Lubbe MS, Serfontein JHP & Truter I. **Drug-drug Interactions between Ritonavir and Other Antiretroviral Drugs in a Private Health Care Sector in South Africa** (Poster Presentation). 68th International Congress of FIP (International Pharmaceutical Federation), Basel, Switzerland, 30 August – 4 September 2008.

Drug-Drug Interactions between Ritonavir and other Antiretroviral Drugs in a Private Health Care Sector in South Africa.

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Background: The introduction of human immunodeficiency virus (HIV) protease inhibitors (PIs) has led to a dramatic decline in the morbidity and mortality associated with HIV infection, though concomitant use of PIs and other antiretrovirals (ARVs) can be complicated by drug-drug interactions (DDIs), adversely affecting levels of PIs.

Objective: To determine the prevalence of possible DDIs between ritonavir and other ARVs in a section of the private healthcare sector in South Africa, for a period of three years.

Study design: A quantitative, retrospective drug utilisation study was performed using data obtained from a medicine claims database during 2004, 2005 and 2006. The data consisted of 2 595 254, 1 621 739 and 993 804 prescriptions claimed during 2004, 2005 and 2006 respectively. The possible DDIs found were identified using the classification by Tatro (2005).

Results: The percentage prevalence of ARV prescriptions claimed increased from 1.92% (n = 43 482) during 2004, to 3.38% (n = 51 613) during 2005 and to 4.73% (n = 47 085) during 2006. A total of 1 326, 1 863 and 960 were possible DDIs identified between ARVs themselves for 2004, 2005 and 2006 respectively. Ritonavir presented with the most possible DDIs accounting for 70.89% (n = 940) for 2004, 13.63% (n = 254) for 2005; and 27.50% (n = 264) for 2006. The highest prevalence of DDIs identified was between ritonavir and indinavir (n = 490, 129, 199) for 2004 to 2006); efavirenz (n = 274, 60) for 2004 and 2006; ritonavir/lopinavir (co-formulated) and efavirenz (n = 118, 88, 65) for 2004 to 2006, nevirapine (n = 49, 37) for 2004 and 2005 and indinavir (n = 9) for only 2004. All were interacting at clinical significance level of 2.

Conclusions: These findings indicate that concomitant use of protease inhibitors like ritonavir, a potent cytochrome P450 (CYP) 3A4 enzyme inhibitor, and other ARVs is complicated by possible DDIs and therefore further studies need to be done on the management of these DDIs.

ABSTRACT: 6.

Katende-Kyenda NL[1], Lubbe MS[2], Serfontein JHP[2], Truter I[3]. **An investigation on possible drug-drug interactions between antiretroviral drugs prescribed in different daily doses and age groups in a private healthcare sector in South Africa** (Oral presentation).

Research Symposium 2008. WSU, 5th & 6th September 2008.

An Investigation on possible Drug-Drug Interactions between Antiretroviral drugs prescribed in different Daily doses and Age-groups in a Private Healthcare Sector in South Africa

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Purpose: The aim of this investigation was to determine possible drug-drug interactions (DDIs) between antiretrovirals (ARVs) prescribed in different daily doses in different age groups, and if the ARVs are prescribed according to the recommended prescribing guidelines in South Africa.

Methods: A quantitave, retrospective drug utilisation study performed on 81096 ARV prescriptions claimed through a medicines claims database during 2006. Possible DDIs between ARVs were identified according to Tatro (2005).

Results: Of the 5728371 patients reviewed, 1.23% was HIV patients, of whom 57.06% were males and 42.94% females. A total of 81096 ARV prescriptions were claimed, of which 4.07% had one item, 43.52% two, 49.56% three, 2.78% four and 0.06% had more than four. A total of 1423 DDIs were identified, of which 50.81% were for 2 drug items, 44.34% three, 3.79% four and 1.05% had more than 4 items. DDIs identified in different age-groups were such that 2.00% were for patients $\leq$ 12 years, 64.57% for patients $>$ 19 years and $\leq$ 45 years, 26.24% for patients $>$ 45 years and $\leq$ 59 years, and 7.18% for patients $<$ 59 years, with patients $>$ 19 years and $\leq$ 45 years having the highest number of DDIs and patients $\leq$ 12 years the lowest. The most important interactions were identified between combinations of: Kaletra (Lopinavir/Ritonavir) and Stocrin (Efavirenz) at daily doses of 799.8 mg/198 mg and 600 mg respectively, followed by Crixivan (Indinavir) and Norvir (Ritonavir) at daily doses of 1600 mg and 200 mg and Kaletra and Nevirapine (Virumune) at 799.8 mg/198 mg and 400 mg daily doses. All the interactions were of clinical significance level 2.

Conclusions:

These results demonstrate the non-adherence of the recommended ARV drug combinations and therefore a need for more education on the prescribing protocols for antiretrovirals.

References: DS Tatro. Drug Interaction Facts. St. Louis, MO: Facts and Comparisons, 1-1699 (2005).

ABSTRACT 7:

Katende-Kyenda NL[1], Lubbe MS[2], Serfontein JHP[2], Truter I[3]. **Factors that influence the prevalence of drug-drug interactions between antiretroviral agents in a healthcare sector in South Africa** (Oral Presentation).

EHRLICH 11 2nd World Conferences on Magic Bullets. Nurnberg, GERMANY, October 3-5, 2008

Factors that influence the prevalence of drug-drug interactions between antiretroviral drugs prescribed to patients of different age groups in a section of private healthcare sector in South Africa.

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Background: Drug-drug interactions (DDIs) are often a serious complication due to taking multiple medications and account for 3% to 5% of all in-hospital medication errors (Leape *et al.*, 1995). DDIs are of particular concern in HIV/AIDs patients receiving highly active antiretroviral therapy (HAART), particularly certain protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), for they interact with other antiretrovirals (ARVs). This is due their metabolism through the cytochrome P450 (CYP450) system.

Aims: 1) To evaluate factors that could influence the prevalence of DDIs between ARVs prescribed in different age groups. 2) To determine whether ARVs were prescribed according to the recommended prescribing guidelines in South Africa. Methods:

This was a quantitative, retrospective drug utilisation study performed on 49 995 (N = 19 860 679) and 81 096 (N = 21 473 074) ARV prescriptions that were prescribed to 43 547 (N = 5 433 440) and 70 719 (N = 5 728 371) HIV patients for 2005 and 2006 and claimed through a medicines claims database. Possible DDIs between ARVs were identified according to Tatro (2005).

Results: Of the 5 433 440 and 5 728 371 patients reviewed for both years, 0.80%; 1.23% was HIV positive patients, of whom 43.26%; 57.06% were males and 56.74%; 42.94% were females for 2005 and 2006 respectively. A total of 49 995; 81 096 ARV prescriptions claimed, of which 4.49; 4.07% had one item, 43.75; 43.52% two, 43.86; 49.56% three, 0.07%; 2.78% four and 0.07%; 0.06% had more than four items on the prescription. Of 811 DDIs identified for 2005, 33.54% were for two drug items, 61.90% three, 2.10% four and 2.46% had more than four items. For 2006, 1115 DDIs were identified, of which 59.64% were for 2 drug items, 27.71% three, 11.12% four and 1.52% had more than 4 items. DDIs identified in different age-groups for 2005 and 2006 were: 5.65% (2006) for patients $\leq$ 12 years, 74.60%; 58.75% for patients > 19 years and $\leq$ 45 years; 23.55%; 27.35% for patients > 45 years and $\leq$ 59 years; and 1.85%; 8.25% for patients $\geq$ 59 years.

The most important interactions were identified between combinations of: Kaletra® (Lopinavir 133.3mg/Ritonavir 33.3mg) and Stocrin® (Efavirenz 600mg) at daily doses of 799.8mg/198mg and 600mg respectively, followed by Crixivan® (Indinavir 400mg) and Norvir® (Ritonavir 100mg) at daily doses of 1600mg and 200mg; and Kaletra® (Lopinavir 133mg/Ritonavir 33.3mg) and Nevirapine (Viramune® 200mg) at 1066.4mg/264.7mg and 400mg daily doses. All the interactions were of clinical significance level 2 (moderate effects), causing deterioration of a patient's clinical status.

Conclusions: These results demonstrate that the non-adherence of the recommended prescribing ARV drug combinations, and daily doses prescribed in different age groups could influence the prevalence of DDIs, therefore a need for more interprofessional education on the prescribing protocols for ARVs.

References

1. Tatro DS. Drug Interaction Facts. St. Louis, Facts and Comparisons, 1-1699 (2005).
2. Leape LL, Bates DW, Cullen DJ et al. Systems analysis of adverse drug events. ADE Prevention Study Group, JAMA, 1995; 274:35-43.

ABSTRACT 8:

Katende-Kyenda NL[1], Lubbe MS[2], Serfontein JHP[2], Truter I[3]. **Evaluation of the prescribed daily dosages as an indicator of possible drug-drug interactions between antiretroviral drugs prescribed to patients of different age groups in a section of private healthcare sector in South Africa** (Oral presentation).

The South African Society for Basic and Clinical Pharmacology and the Southern African Neuroscience Society Congress. 5-8 October 2008. Grahamstown.

Evaluation of the prescribed daily dosages as an indicator of possible drug-drug interactions between antiretroviral drugs prescribed to patients of different age groups in a section of private healthcare sector in South Africa.

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Purpose :
The aim of this study was to evaluate average prescribed daily doses (PDDs) as an indicator of possible DDIs between ARVs prescribed in different age groups, and to determine whether these ARVs were prescribed according to the recommended prescribing guidelines in South Africa.

Methods:
This quantitative, retrospective drug utiisation study was performed on 49 995 (N = 8 506 355) and 81 096 (N = 9 029 912) ARV prescriptions that were prescribed to 7664 (N = 1 218 358) and 10 162 (N = 1 259 099) HIV patients for 2005 and 2006 and claimed through a medicines claims database. Possible DDIs between ARVs were identified according to Tatro.[18]

Results: The results revealed that 4.49% and 4.07% of the ARV prescriptions for 2005 and 2006 respectively had one ARV medicine item, 43.75% and 43.52% had two, 43.86% and 49.56% had three, 0.07% and 2.78% had four and 0.07% and 0.06% had more than four ARV medicine items on the prescription. Of 811 DDIs identified for 2005, 33.54% were for two ARV medicine items, 61.90% three, 2.10% four and 2.46% had more than four items. For 2006, 1115 DDIs were identified, of which 59.64% were for two ARV medicine items, 27.71% three, 11.12% four and 1.52% had more than four ARV medicine items. DDIs identified in different age groups for 2005 and 2006 were: 0%; 5.65% for patients ≤ 12 years, 74.60%; 58.75% for patients > 19 years and ≤ 45 years; 23.55%; 27.35% for patients > 45 years and ≤ 59 years; and 1.85%; 8.25% for patients > 59 years.

The most important interactions were identified between combinations of: Kaletra® (Lopinavir 133.3mg/Ritonavir 33.3mg) and Stocrin® (Efavirenz 600mg) at average prescribed daily doses of 799.8mg(Lopinavir)/198mg(Ritonavir) and 600mg (Efavirenz) respectively, followed by Crixivan® (Indinavir

400mg) and Norvir® (Ritonavir 100mg) at average PDDs of 1600mg and 200mg; and Kaletra® (Lopinavir 133mg/Ritonavir 33.3mg) and Viramune® 200mg(Nevirapine 200mg) at 1066.4mg(Lopinavir)/264.7mg (Ritonavir) and 400mg Nevirapine average PDDs. All the interactions were of clinical significance level 2 (moderate effects), causing deterioration of a patient's clinical status.

Conclusion:

These results demonstrate that some ARVs were not prescribed according to the recommended average prescribed daily doses and drug combinations; therefore a need for more education on the prescribing protocols for ARVs in the treatment of HIV infected patients was identified.

ABTRACT 9:

Katende-Kyenda NL, Lubbe MS, Serfontein JHP, Truter I. **Prevalence of antiretroviral drug-drug interactions between antiretroviral regimens as prescribed according to the recommended antiretroviral dosing.** (Poster presentation).

5th International Conference on Pharmaceutical and Pharmacological Sciences (ICPPS)- 2009. North-West University, Potchefstroom Campus, 23-26 September 2009.

Prevalence of antiretroviral drug-drug interactions between antiretroviral regimens as prescribed according to the recommended antiretroviral dosing

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Purpose:

The aim of this investigation was to determine the prevalence of drug-drug interactions (DDIs) between antiretrovirals (ARVs) and if prescribed according to or/not the recommended dosages for antiretroviral agents and according to patients' age.

Methods:

A quantitative, retrospective drug utilisation study was performed on 49 995, 81 096 and 88 988 ARV prescriptions prescribed to 7 664, 10 162, and 10 061 human immunodeficiency (HIV) patients for 2005, 2006 and 2007 and claimed through a pharmacy benefit management company. Potential DDIs between ARVs were identified and dosages evaluated according to guidelines indicated in the literature and treatment guidelines.

Results:

The results revealed that 4.49%, 4.07% and 2.99% of the ARV prescriptions for 2005, 2006 and 2007 respectively had one ARV item, 43.77%, 43.52%, and 55.70% had two items; and 51.76%, 51.93% and 43.38% had three or more ARV items. The total number of DDIs according to age group for the three years was 779 (2005), 1 155 (2006) and 1 177 (2007) respectively, of which 4.37%, 2.94% and 2.55% were prescribed to patients 0<=12 years, 1.03%, 0.00% and 0.42% to patients 12<=19 years and 69.28%, 67.97% and 69.24% to patients 19<=45 years and 25.32%, 29.09% and 27.79 to patients 45<=59 years and older.

The most prevalent antiretroviral drug regimens that were prescribed not according to the recommended ARVs dosing and where DDIs were identified according to patients' age were: Lopinavir/ritonavir 800mg/200mg and Efavirenz 200mg prescribed to patients **0<=12 years** (n = 20), Lopinavir/ritonavir 320mg/80mg and Nevirapine 2600mg (n = 8). Then Lopinavir/ritonavir 1066.4mg/264mg and Efavirenz 600mg to patients **19<=45 years** (n = 347), Lopinavir/ritonavir 1066.4mg/264mg and Nevirapine 400mg (n = 41), Indinavir 1600mg and Ritonavir 800mg (n = 16). Then Lopinavir/ritonavir 1066.4mg/264mg and Efavirenz 600mg to patients **45<=59 years** (n = 49), Lopinavir/ritonavir 1066.4mg/264mg and Efavirenz 600mg (n = 22), Lopinavir/ritonavir 1066.4mg/264mg and Efavirenz 400mg

(n = 7), Lopinavir/ritonavir 1066.4mg/264mg and Nevirapine 500mg (n = 10), Saquinavir 800mg and Ritonavir 800mg (n = 18); Then Lopinavir/ritonavir 1066.4mg and Nevirapine 400mg to patients **>59 years** (n = 3), Lopinavir/ritonavir 1066.4mg/264mg and Efavirenz 600mg (n = 9), Lopinavir./ritonavir 1066.4mg/264mg and Efavirenz 500mg (n = 2).

Conclusion and Recommendation:

Drug-drug interactions were identified between ARVs prescribed in different age groups, age group 3(19<=45), furthermore there were identified in ARV regimens with Prescribed Daily Doses that were not according to the recommended ARV dosing. There is need for more education to prescribers to adhere to the recommended standard dosing for ARVs for HIV/AIDS patients to achieve maximum virological suppression and lower costs in terms of possible adverse effects

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Date: 25 Sep 2009